IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PERSONAL GENOMICS TAIWAN, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 19-1810 (VAC) (MPT)
	)	
PACIFIC BIOSCIENCES OF CALIFORNIA, INC.,	)	
	)	
	)	
Defendant.	)	

JOINT CLAIM CONSTRUCTION BRIEF

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August 10, 2022

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In accordance with the Revised Scheduling Order (D.I. 49), and Stipulation and Order to Extend Time (D.I. 69), Plaintiff Personal Genomics Taiwan, Inc. ("PGI") and Defendant Pacific Biosciences of California, Inc. ("PacBio") submit their Joint Claim Construction Brief for U.S. Patent No. 7,767,441 ("the '441 patent"), which PGI is asserting against PacBio.

I. INTRODUCTIONS

A. Plaintiff's Opening Position

The parties have identified two disputed claim terms in this matter: (1) the preamble of independent claim 1, which is incorporated into all of the asserted claims and recites: "An apparatus for identifying a single biomolecule;" and (2) "blocked and labeled nucleotides," which is found in a handful of dependent claims. *See* D.I. 56 (Joint Claim Construction Chart).

This Court need not wade into the merits of the preamble dispute because the parties already litigated the construction of the preamble in IPR2020-01200 and the Patent Trial and Appeal Board ("PTAB") ultimately issued a Final Written Decision ruling against PacBio's position. Issue preclusion therefore applies, and PacBio is estopped from collaterally attacking the PTAB's construction of the preamble in this Court.

If the Court does address the merits of the preamble, it should reject PacBio's positions just as the PTAB did. PacBio contends that the preamble is not limiting. But the preamble of claim 1 is a textbook example of a claim limitation under controlling Federal Circuit authority. It provides antecedent basis for a term in the bodies of the claims and also recites what the specification describes as a fundamental characteristic of the invention: identifying a single biomolecule. The Background, Summary, and Detailed Description, for example, repeatedly underscore the single-molecule nature of the invention. All of the Examples describe apparatuses for detecting a single biomolecule and methods for making and using them, and all of the apparatuses of the figures are expressly identified as structures for identifying a single

biomolecule. Moreover, the specification distinguishes identifying a single biomolecule from detecting signals from multiple biomolecules in a cluster or ensemble. Thus, a person having ordinary skill in the art would have understood that "[a]n apparatus for identifying a single biomolecule" is capable of detecting a signal associated with an individual biomolecule.

As for "blocked and labeled nucleotides," no construction is required because the term should be given its plain and ordinary meaning. If the Court nevertheless decides to construe the term, PacBio's proposed construction should be modified to make it consistent with the specification of the '441 patent.[1]

B. Defendant's Answering Position

1. Introduction

There are two disputed claim terms:

1. "An apparatus for identifying a single biomolecule" (claim 1 preamble, all asserted claims)
2. "blocked and labeled nucleotides" (claims 21, 22, and 24)

D.I. 42-1 ("'441 patent") at claims 1, 21, 22, and 24. As documented below, PGI's positions as to both terms are at odds with the intrinsic evidence and violate several fundamental canons of claim construction. They should not be adopted.

Indeed, as to the first term, PGI's lead position is to try and convince the Court to ignore the substance, arguing that there is collateral estoppel because the Patent Trial and Appeal Board ("PTAB") allegedly adopted PGI's construction in an IPR proceeding. PGI, however, fails to

[1] Because the Scheduling Order provides that the claim construction briefing "need not include any general summaries of the law relating to claim construction," D.I. 13 at 10, *see also* D.I. 49 (modifying only the schedule of D.I. 13), this opening brief does not address the basic principles of claim construction.

inform the Court that the construction it is now advocating is ***different*** from what it presented to the PTAB and involves language very different from what the PTAB ultimately adopted. Collateral estoppel thus does not apply. Moreover, this and other courts have repeatedly held that a PTAB claim construction by itself does not trigger issue preclusion. PGI does not cite a single case where a district court gave preclusive effect to a PTAB claim construction that has not yet been affirmed on appeal.

As to the merits, whereas the claims refer broadly to "identifying a single biomolecule," PGI seeks to drastically narrow this language and impose a requirement that claimed systems be capable of "identifying" a biomolecule by a particular technique, specifically, by detecting a signal from an "individual biomolecule." PGI thus seeks to exclude from the scope of the claims systems that identify a molecule by first copying it and detecting a signal from the resulting ensemble of identical molecules. Regardless, PGI's major alteration of the claim language should raise an immediate red flag as to the merits of its proposed construction.

While nothing in the preamble as drafted imposes the capability of detecting signal from an individual biomolecule, the dependent claims and specification prove definitively that it would be wrong to interpret the preamble as imposing such a capability. Specifically, dependent claims recite that the molecule of interest is "amplified" (i.e., copied) or that "one or more" molecules are placed at the detection site. If the molecule is copied before detection, or if more than one molecule is placed at the detection site, the claims (including the language of the preamble as drafted) cannot possibly be understood to require detection of a signal from a single, individual biomolecule and must encompass "identifying a single biomolecule" by detecting a signal from multiple molecules. It is unsurprising that the patent includes such dependent claims because, as shown herein, the specification expressly discloses embodiments based on the detection of signal from multiple

molecules for use with the alleged "invention." Nowhere does the specification disavow coverage of systems incapable of detecting signal from an "individual biomolecule."

PGI's brief, however, ignores both the dependent claims and the corresponding embodiments, which is perhaps unsurprising given what took place in the IPR. There, to the extent PGI even attempted to rebut this important intrinsic evidence, its own expert admitted that PGI's theories were based on "speculation" and a creative interpretation of the claims that he would not vouch for as a "strategy that was in the mind of the people who wrote the '441 patent." *See* Ex. 6 at 118:12-119:9 (JA 429). At bottom, PGI's construction is an improper attempt to limit the claims to preferred embodiments, absent any lexicography, disavowal, or disclaimer that would otherwise justify this.

As to the term "blocked and labeled nucleotides," PGI takes the complete opposite approach relative to its approach for the preamble. Whereas PGI seeks to drastically narrow the preamble, even though it consists of plain and ordinary language that is easily understood by a lay jury, PGI inexplicably contends that "blocked and labeled nucleotides" should be given its "plain an ordinary meaning," even though it is a highly technical term that a lay jury would not understand in the slightest. PGI's request to let the jury speculate should be rejected. The specification confirms PacBio's construction because it makes clear that "blocked" nucleotides are those that prevent further extension of a DNA strand during DNA sequencing. PGI does not truly dispute this, but instead contends that PacBio's construction is wrong because if a "blocked and labeled" nucleotide were "modified" so that it is no longer "blocked," it would allow base extension. PGI's assertion that PacBio's construction is wrong because it does not capture the capabilities of chemical compounds that are not actually the compounds in question, but rather compounds that are "modified" to make them into different things, makes little sense and should be rejected.

Accordingly, and for the additional reasons stated below, the Court should adopt PacBio's proposed constructions.

2. Technology Background

(a) Overview Of Molecular Detection Techniques

At the time of filing, molecular detection technologies, including for DNA sequencing, had been well-developed. A basic understanding of the key approaches in use at the relevant time is important background for the claim construction dispute related to the preamble.

First, technology for simply imaging a single, individual molecule had been established, as confirmed by Dr. Timothy Harris, PGI's expert in the IPRs. As he explained, there were "hundreds and hundreds" of publications on this topic:

> Q. Okay. So you agree that the inventors of the '441 patent were not the first to invent single molecule sequencing?
>
> A. That the prior – there was prior single molecule sequencing art that had been disclosed publicly in – in seminar presentations before the priority date of that patent.
>
> Q. The inventors of the '441 patent were not the first to invent dete[c]tion of single molecules then; correct?
>
> A. Dete[c]tion of single molecules predates that patent by more than twenty years.
>
> * * *
>
> I was aware of DNA sequencing and single-molecule strategy for DNA sequencing as early as 1981. They were widely discussed subjects at virtually every conference I attended.
>
> * * *
>
> There are – there are hundreds and hundreds of publications of single molecule imaging that are successfully achieved and, therefore, it does not surprise me that they don't dwell on the difficulty of doing single molecule imaging.

Ex. 6 at 20:3-17, 35:3-6, 71:2-6 (JA 404, 408, 417).

Second, at the relevant time frame, another widely-used approach was based on analyzing an ensemble of molecules consisting of a collection of molecules of the same species. This approach was particularly applicable in the rapidly emerging field of DNA sequencing, where techniques such as polymerase chain reaction were available to quickly copy (i.e., amplify) a DNA molecule. The straightforward idea behind this approach was to first copy the DNA molecule and then detect an enhanced signal that arises from multiple copies of the molecule.

This was described, for instance, in a 2004 review of DNA sequencing methods by Shendure et al., which provided an overview of an approach to sequencing known as "Cyclic-Array Sequencing on Amplified Molecules:"

> An additional uniting feature of these methods — one that distinguishes them from several of the single molecule projects that are discussed below — is that all rely on some method of isolated (that is, clonal) amplification. After amplification, each feature to be sequenced contains thousands to millions of copies of an identical DNA molecule, although features must be spatially distinguishable. The amplification is necessary to achieve sufficient signal for detection.

Ex. 7 at 340 (JA 512). The '441 patent incorporates by reference the Shendure reference specifically for its teaching of sequencing approaches for use with the invention. '441 patent at 12:36-40, 18:51-54.

One widely used DNA sequencing technology that fits the foregoing description is the Illumina sequencing platform. *See* Ex. 6 at 86:16-25 (JA 421). As PGI's expert confirmed, this sequencing platform was discussed at "virtually every conference" he attended in the relevant time frame because it was "commercially important and scientifically important:"

> Q. Okay. When did you personally first become aware of the Illumina sequencing platform?
>
> A. I was aware of Illumina and all of its corporate antecedents from their very inception.

When their currently available bridge PCR amplification became available to anyone outside, I do not have an answer.

Q. How was it that you were aware of Illumina and its corporate antecedents?

A. My field of investigation in measurement technology from – from 1980 on had a lively conversation about methods to enhance sequencing performance and throughput.

I was aware of DNA sequencing and single-molecule strategy for DNA sequencing as early as 1981. They were widely discussed subjects at virtually every conference I attended.

Q. And why was that?

A. Because they're commercially important and scientifically important technologies.

* * *

Q. Was if fair to say that during your time at Helicos, Illumina and its corporate antecedents were discussed at virtually every conference you attended?

A. Yes.

Q. And again you were at Helicos when?

A. January 2004 to August 2008.

Ex. 6 at 34:15-35:9, 35:19-24 (JA 408).

As documented below, PGI drafted not just its claims, but also its specification, broadly to ensure that its claims would cover approaches based not just on detecting signals from single, individual molecules, but also the widely-used ensemble approaches that were both commercially and scientifically important and being discussed at every scientific conference at the time.

(b) Overview Of The ’441 Patent

The ’441 patent pertains to a general-purpose sensor for biomolecules, such as DNA:

> The present invention relates to a bioassay system including a plurality of optical detection apparatuses, and uses of the bioassay system for detecting and analyzing biomolecules, such as nucleic acids. More particularly, the present invention relates to a bioassay system including at least ten thousand optical detection apparatuses for monitoring, in some embodiments, a large number of fluorophore molecules in parallel for detecting and analyzing the biomolecules.

'441 patent at 1:15-22. One application the '441 patent suggests is appropriate for the alleged invention is DNA sequencing. *See id.* at 2:52-54 ("In some embodiments the nucleic acid is detected by performing nucleic acid sequencing on the optical detection apparatus.").

Independent claim 1 sets forth the basic components of the alleged invention of the '441 patent and is as follows:

> 1. An apparatus for identifying a single biomolecule, comprising:
>
> a substrate having a light detector; and
>
> a linker site formed over the light detector, the linker site being treated to affix the biomolecule to the linker site;
>
> wherein the linker site is proximate to the light detector and is spaced apart from the light detector by a distance of less than or equal to 100 micrometers.

'441 patent and claim 1. On its face, there is nothing novel or inventive in this claim. Biomolecules are affixed to a "linker site" on a surface, either through direct attachment or via an intermediary binding molecule. Once affixed, the molecules are detected by a light detector. The emitted light is analyzed for molecular identification purposes, such as DNA sequencing. These features are recited at a completely generic level, undermining any contention that they confer novelty. The Board concluded in IPR2020-01163 that this claim is invalid. *See* Ex. 20 (JA 821-84).

While claim 1 refers to "identifying a single biomolecule," the dependent claims confirm that this "identifying" need not take place via detection of a signal from a single, individual biomolecule. Claim 26, for instance, recites that the "nucleic acid" (*e.g.*, DNA) is "amplified" before sequencing, thus making clear that signal is detected from more than one molecule:

> 26. The method of claim 16, wherein the nucleic acid is ***amplified*** at the linker site before nucleic acid sequencing.

'441 patent at claim 26. Likewise, claim 30 recites that more than one molecule can be attached to the linker site, proving that the claims cover detection of signal from more than one molecule:

> 30. A method of detecting a biomolecule, comprising the steps of: affixing ***one or more*** biomolecule to the linker site of the apparatus of claim 1; and detecting the biomolecule on the apparatus.

'441 patent at claim 30.

The '441 patent issued only because the Examiner gave the claims no scrutiny. During prosecution, for instance, the Examiner conducted a prior art search focused on the terms "nanopore" and "nanochannel," neither of which is mentioned anywhere in the '441 patent nor recited in the claims. *See* Ex. 8 (JA 518-25). Likewise, the Examiner searched for "tetraethylorthosilicate," an irrelevant chemical compound that is again not mentioned in the specification let alone the claims. *Id.* After conducting this defective prior art search, the Examiner allowed the claims without issuing a single rejection.

To the extent any point of novelty was identified, it was supposedly in the placement of the linker site "proximate" to the detector such that the linker site and detector are 100 μm or less apart. According to the '441 patent, "existing devices do not place the molecule being detected in close proximity to a corresponding detecting unit, which substantially limits the strength of the detected signal." '441 patent at 1:57-60. This distance feature was the primary reason the Examiner allowed the claims:

> The primary reason for allowance of independent claims 1, 10 and 61 and their dependent claims is the inclusion of the limitations, as found in combination in the claims, of a light detector spaced a distance of less than or equal to 100 micrometers from a linker site that is treated to affix a biomolecule. The prior art does not teach spacing a detector and linker site at the claimed range of distance nor does it provide a motivation to arrive at such a range.

Ex. 8 at 3 (JA 524). Nowhere during prosecution was the detection of signal from a single, individual biomolecule identified as a point of novelty that distinguished the claims from the prior art.

C. Plaintiff's Reply Position

PacBio does not dispute that the construction of the preamble of claim 1 was (1) previously adjudicated by the PTAB; (2) actually litigated by the parties, who were fully represented in the prior action and had a full and fair opportunity to litigate how the preamble should be construed; and (3) necessary to the PTAB's Final Written Decision, which was a final and valid judgment. Nonetheless, PacBio argues that issue preclusion/collateral estoppel does not apply because "the construction [that PGI] is now advocating is ***different*** from what it presented to the PTAB." Joint Brief at 2-3. PacBio misidentifies the relevant "issue" as the construction that PGI initially proposed to the PTAB. But the "issue," for issue preclusion purposes, is the proper construction of the preamble, ***which the PTAB decided in its Final Written Decision***. To whatever extent PGI's proposed construction is different from what it presented to the PTAB, it is different only because PGI conformed its proposal to the PTAB's ruling, which should have issue preclusive/collateral estoppel effect.

PacBio obviously disagrees with the PTAB's ruling. But PacBio can raise its disagreements in the appeal it filed with the Federal Circuit. Issue preclusion prevents PacBio from collaterally attacking the PTAB's ruling in this Court.

PacBio argues that because its appeal to the Federal Circuit is still pending, it is free to re-litigate the same claim construction issue here. But "[t]he law is well settled that the pendency of an appeal has no effect on the finality or binding effect of a trial court's holding." *Pharmacia & Upjohn Co. v. Mylan Pharms., Inc.*, 170 F.3d 1373, 1381 (Fed. Cir. 1999). PacBio identifies no exception for Final Written Decisions from the PTAB, and none of the cases cited by PacBio holds that issue preclusion cannot attach to a Final Written Decision from the PTAB until it has been

subject to appellate review. Accordingly, issue preclusion applies and this Court need not address the substance of how the preamble of claim 1 should be construed.

On the merits, PacBio contends that PGI "seeks to drastically narrow [the claim] language and impose a requirement that claimed systems be capable of 'identifying' a biomolecule by a particular technique, specifically, by detecting a signal from an 'individual biomolecule.'" Joint Brief at 3. But the claims themselves dictate this alleged "technique" because they expressly require "[a]n apparatus for identifying a ***single*** biomolecule." Accordingly, there is no need for the patent to "disavow coverage of systems incapable of detecting signal from an 'individual biomolecule.'" Joint Brief at 3-4. PacBio accuses PGI of proposing a "major alteration of the claim language," but again, PGI's proposed construction simply reflects the PTAB's claim construction ruling, which it based on a detailed review of the claim language and the rest of the intrinsic record for the '441 patent.

PacBio nowhere disputes that the specification of the '441 patent repeatedly emphasizes single-molecule detection, that all of the apparatuses in the figures are expressly identified as structures for identifying a single biomolecule, that all of the "Examples" in the patent describe apparatuses for detecting a single biomolecule and methods for making and using them, and that the specification is elsewhere replete with references to identifying a single biomolecule.

PacBio argues that "the dependent claims and specification prove definitively that it would be wrong to interpret the preamble as imposing [] a capability" of "detecting a signal from an individual biomolecule." Joint Brief at 3. But the dependent claims in no way suggest that the apparatus of claim 1 need ***not*** be capable of detecting a signal associated with an individual biomolecule. Nor do they even describe detecting signals from multiple identical biomolecules. PacBio relies on dependent method claims 26 and 30. Claim 26 recites amplifying a nucleic acid,

not detecting a signal from multiple identical nucleic acids. Claim 30 simply recites affixing to the linker site "one or more" biomolecules—which can include a biomolecule such as polymerase that links to a substrate a different biomolecule, such as a nucleic acid to be sequenced or otherwise identified.

PacBio asserts that it must be inferred from claims 26 and 30 that a signal from multiple identical biomolecules is detected. But no such inference is justified. As PGI's expert explained, the methods of both claims can be used with an apparatus that detects a signal associated with an individual biomolecule. The PTAB properly credited this testimony, which is consistent with the written description and claim language. Ex. 1 at 20 (JA at 44). PacBio criticizes the expert because he acknowledged that the inventors "didn't describe how they were going to take advantage of the amplification process" of claim 26, Joint Brief at 38-39, and because for that reason he referred to possible ways to take advantage of it as "speculative" and appropriately noted that he "would not vouch for [a particular way] as a 'strategy that was in the mind of the people who wrote the '441 patent.'" Joint Brief at 4. PacBio never establishes as non-"speculative" the theoretical possibility of affixing to the same linker site all of the biomolecules produced through amplification. Nor does PacBio justify its outright speculation that the inventors actually had in mind such an approach.

PacBio contends that "the specification expressly discloses embodiments based on the detection of signal from multiple molecules for use with the alleged 'invention.'" Joint Brief at 3-4. But the alleged "embodiments" identified by PacBio are descriptions in materials incorporated by reference, and the patent cites those materials for their disclosures of sequencing modalities, not for the numbers of molecules to which those modalities are applied. The modalities themselves can be applied to sequence either a single molecule or multiple molecules together. For all of these reasons, PGI's construction of the preamble should be adopted.

As for "blocked and labeled nucleotides," the parties appear to agree that "blocked and labeled nucleotides" used for "base extension sequencing," as recited in claim 21, are designed to be modified so as to permit further cycles of base extension. PGI would agree to PacBio's construction with the addition of "absent modification" to the end of it.

II. AGREED-UPON CONSTRUCTIONS

The parties have not agreed upon any constructions.

III. DISPUTED CONSTRUCTIONS

A. "An apparatus for identifying a single biomolecule" (preamble)

Claim Term	PGI's Position	PacBio's Position
"**An apparatus for identifying a single biomolecule"** (all asserted claims)	The preamble is limiting. "An apparatus for identifying a single biomolecule" is capable of detecting a signal associated with an individual biomolecule, as opposed to multiple identical biomolecules."	The preamble is not limiting. No construction necessary.

1. Plaintiff's Opening Position

The term "[a]n apparatus for identifying a single biomolecule" appears in independent claim 1, which recites:

> 1. An apparatus for identifying a single biomolecule, comprising:
> a substrate having a light detector; and
> a linker site formed over the light detector, the linker site being treated to affix the biomolecule to the linker site;
> wherein the linker site is proximate to the light detector and is spaced apart from the light detector by a distance of less than or equal to 100 micrometers.

All of the asserted claims depend from, or otherwise incorporate, claim 1.

(a) PacBio is estopped from collaterally attacking the construction of the preamble in this Court.

"[W]hen an issue of fact or law is actually litigated and determined by a valid and final judgment, and the determination is essential to the judgment, the determination is conclusive in a subsequent action between the parties, whether on the same or a different claim." *B&B Hardware, Inc. v. Hargis Indus., Inc.*, 575 U.S. 138, 148 (2015). This is the bedrock doctrine of "issue preclusion," also known as "collateral estoppel," which has been discussed extensively in Supreme Court cases dating back to the 19th century.

In *Southern Pacific Railroad Co. v. U.S.*, for example, Justice Harlan cited multiple cases illustrating the rule that "a right, question or fact distinctly put in issue, and directly determined by a court of competent jurisdiction, as a ground of recovery, cannot be disputed in a subsequent suit between the same parties or their privies; and, even if the second suit is for a different cause of action, the right, question, or fact once so determined must, as between the same parties or their privies, be taken as conclusively established, so long as the judgment in the first suit remains unmodified." 168 U.S. 1, 48-49 (1897).

"[I]ssue preclusion is not limited to those situations in which the same issue is before two *courts*." *Id.* Rather, "where a single issue is before a court and an administrative agency, preclusion also often applies." *Id.* Indeed, the Federal Circuit recently noted: "[W]e have already held that issue preclusion applies to inter partes reviews." *SynQor, Inc. v. Vicor Corp.*, 988 F.3d 1341, 1347 (Fed. Cir. 2021) (citation omitted); *see also id.* at 1353 (noting "our application of collateral estoppel to inter partes reviews"); *SkyHawke Techs., LLC v. Deca Int'l Corp.*, 828 F.3d 1373, 1376 (Fed. Cir. 2016) ("[A]dministrative decisions by the U.S. Patent and Trademark Office can ground issue preclusion in district court when the ordinary elements of issue preclusion are met.").

There are four standard requirements for the application of issue preclusion: "(1) the identical issue was previously adjudicated; (2) the issue was actually litigated; (3) the previous determination was necessary to the decision; and (4) the party being precluded from relitigating the issue was fully represented in the prior action." *Jean Alexander Cosmetics, Inc. v. L'Oreal USA, Inc.*, 458 F.3d 244, 249 (3d Cir. 2006). Courts also consider whether the party opposing issue preclusion had a "full and fair opportunity" to litigate the issue, and whether that issue was decided by a "final and valid judgment," *id.*, which includes not only a appealable decisions, but also "any prior adjudication of an issue in another action that is determined to be sufficiently firm to be accorded conclusive effect." *In re Brown*, 951 F.2d 564, 569 (3d Cir. 1991) (quoting 1 *Restatement (Second) of Judgments* § 13 (1982)).

All of these considerations favor the application of issue preclusion in this case based on the PTAB's Final Written Decision in IPR2020-01200.

(i) The PTAB construed the preamble of claim 1.

The PTAB already adjudicated the identical issue that PacBio is now seeking to re-litigate here: whether the preamble of claim 1 is limiting and, if so, what it means.

In IPR2020-01200, PacBio argued that the preamble is not limiting and that "[a]n apparatus for identifying a single biomolecule" need not be capable of detecting a signal associated with an individual biomolecule. *Pacific Biosciences of California, Inc. v. Personal Genomics Taiwan, Inc.*, IPR2020-01200, Paper 31 at 18 (P.T.A.B. Jan. 18, 2022) (Final Written Decision) (Ex. 1) (JA 42). After reviewing the intrinsic evidence, the Board found "inapposite" PacBio's argument that the preamble was not limiting and "that one can 'identify' a single molecule from a signal from multiple copies of the same molecule." *Id*. The Board concluded that:

> [W]e determine that the preamble of claim 1 is limiting, requires an apparatus capable of identifying a single biomolecule, and provides antecedent basis for "the

> biomolecule" as used in the body of the independent claims, which should be read as "the single biomolecule" introduced in the preamble.

Id. at 21. Here, just as it did in IPR2020-01200, PacBio is arguing that the preamble is not limiting and that "[a]n apparatus for identifying a single biomolecule" need not be capable of detecting a signal associated with an individual molecule. Thus, the issue decided by the PTAB against PacBio in IPR2020-01200 was identical to the issue PacBio seeks to re-litigate here.

(ii) PacBio, which was a party to the PTAB proceeding, vigorously litigated the construction of the preamble of claim 1.

PacBio was a party to IPR2020-01200 and used the same counsel as in the current proceedings before this Court. *Compare* Ex. 2 at 6 (JA 95) *with* D.I. 15. Fully represented, PacBio had a full and fair opportunity to litigate—and actually litigated—the construction of the preamble during IPR2020-01200, vigorously contesting the issue at multiple points in the IPR proceedings. *See, e.g.*, Ex. 2 (PacBio's Petition in IPR2020-01200) at 16-18 (arguing that the preamble is not limiting, and that even if were, "the claims also encompass the detection of a signal arising from multiple molecules of the same species") (JA 105-07); Ex. 3 (PacBio's Reply in IPR2020-01200) at 2-4 (arguing that "'[i]dentifying' what a molecule is does not require detecting a signal from only a single individual molecule") (JA 179-81).

(iii) The PTAB's construction of the preamble was necessary to its decision upholding the validity of the challenged claims.

Each of PacBio's grounds of unpatentability in IPR2020-01200 relied on one of two prior art references—"Hassibi" or "Blumenfeld." IPR2020-01200, Paper 31 at 6 (Final Written Decision) (JA 25-76). Based on its construction of the preamble of claim 1, the PTAB decided that neither of these references discloses an apparatus that is capable of identifying a single biomolecule. *See id.* at 32 ("We determine that Hassibi fails to disclose an apparatus that is capable

of identifying a single biomolecule.") (JA 56); *id.* at 49 ("[W]e find that Blumenfeld does not teach an apparatus for identifying a single biomolecule as required by all challenged claims.") (JA 73). Thus, the construction of the preamble of claim 1 was necessary to the PTAB's judgment, "as it was part and parcel of the PTAB's determination" that PacBio failed to establish that the challenged claims are unpatentable. *Princeton Dig. Image Corp. v. Konami Dig. Entm't, Inc.*, No. 12-cv-1461, 2017 WL 2615739 at *4 (D. Del. June 16, 2017) (finding claim construction issue regarding means plus function term decided by the PTAB was essential to the judgment, where the PTAB found "[s]everal terms [including this one] relevant to this decision are means-plus-function claim terms"), *reported and recommendation adopted in relevant part*, 2017 WL 6375173 (D. Del. Dec. 13, 2017).

(iv) The PTAB's Final Written Decision is a valid and final judgment.

As noted above, the PTAB construed the preamble of claim 1 in a Final Written Decision finding the challenged claims unpatentable after PacBio had a full and fair opportunity to litigate—and actually litigated—the issue. *See* Joint Brief at 14-17. The Final Written Decision is a reasoned opinion issued after PacBio was fully heard in the proceeding. *See, e.g.*, IPR2020-01200, Paper 31 (Final Written Decision) (JA 25-76). And although issue preclusion "does not require the entry of a judgment, final in the sense of being appealable," *In re Brown*, 951 F.2d at 569, the PTAB's decision here not only was appealable, 35 U.S.C. § 319, it was in fact appealed by PacBio. D.I. 41 at 2.

The pending appeal does not defeat the application of issue preclusion. For example, citing Supreme Court authority,[2] the Federal Circuit has noted "the law is well settled that the pendency

[2] *Deposit Bank v. Board of Councilmen of City of Frankfort*, 191 U.S. 499 (1903).

of an appeal has no effect on the finality or binding effect of a trial court's holding." *Pharmacia & Upjohn Co. v. Mylan Pharms., Inc.*, 170 F.3d 1373, 1381 (Fed. Cir. 1999) (citation omitted).

In *Pharmacia*, a district court gave preclusive effect to a decision from another tribunal concerning the validity and enforceability of a patent. *Id.* at 1379. The decision was subject to a pending "JMOL/new trial motion" and, by the time *Pharmacia* reached the Federal Circuit, subject to its own pending appeal. *Id.* The collaterally estopped party argued to the Federal Circuit that "the application of collateral estoppel was premature based on the 'uncertainty' of the [tribunal's] judgment." *Id.* The Federal Circuit rejected that argument and found that the district court properly accorded the "judgment full collateral estoppel effect," noting "[t]he established rule in the federal courts . . . that a final judgment retains all of its res judicata consequences pending decision of the appeal." *Id.* at 1381 (citing 18 Charles Alan Wright et al., *Federal Practice and Procedure*, § 4433, at 308 (1981)).

Accordingly, district courts continue to "apply collateral estoppel based on another district court's decision when that preclusive decision is on appeal or an appeal is imminent." *See, e.g.*, *Biogen Int'l GmbH, v. Amneal Pharms.*, 487 F. Supp. 3d 254, 267 (D. Del. 2020) (according a judgment that was pending appeal full collateral estoppel effect); *Galderma Labs., Inc. v. Amneal Pharms., LLC*, 921 F. Supp. 2d 278, 280-82 (D. Del. 2012); *XR Commc'ns. v. D-Link Sys.*, 2022 U.S. Dist. LEXIS 25984, at *11-15 (C.D. Cal. Jan. 4, 2022) (applying collateral estoppel based on judgment of invalidity where underlying claim construction order was being appealed).

In *Galderma*, the court applied collateral estoppel based on a finding of non-infringement in a previous action (the "*Mylan* Action") despite the fact that an appeal of the prior judgment was pending. 921 F. Supp. 2d at 280-82. Galderma argued collateral estoppel should not apply pending appeal because of the possibility that "the Federal Circuit will address claim construction of

[certain terms] . . . in the Mylan Appeal, and that the Federal Circuit's ruling on this issue will guide or possibly control the issue of [] patent infringement in this action." *Id.* at 281. The court rejected Galderma's argument, explaining that "unless or until such a ruling is handed down by the Federal Circuit, this Court's judgment in the *Mylan* Action has effect." *Id.* Here too, the PTAB's judgment should be accorded full collateral estoppel effect as PacBio pursues its appeal.

* * *

In sum, collateral estoppel precludes PacBio from re-litigating the construction of the preamble before this Court. The Court should therefore adopt PGI's proposed construction, consistent with the PTAB's decision in IPR2020-01200.

(b) If this Court considers the merits, it should reject PacBio's position.

(i) Background of the '441 Patent

The '441 patent discloses apparatuses and methods for identifying a **single** biomolecule affixed to an apparatus, as exemplified below in FIG. 2 (color added), which shows in cross-section single DNA molecule 32 (blue) with chromophore 36 (yellow) over detector 210 (green).

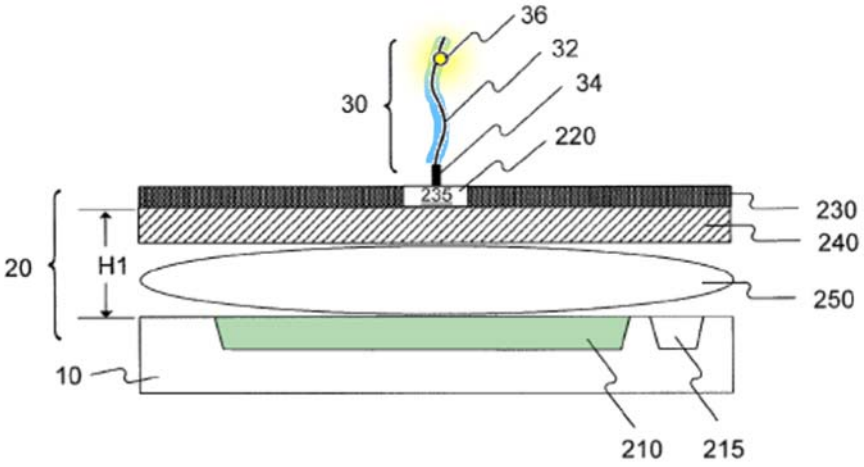


Figure 1: *Detecting a signal from a single biomolecule.*

This differs significantly from the alleged prior art, which, as PacBio itself has repeatedly explained, describes detecting a spot on an array, where "each spot on the array contains probes

specific for a particular molecular species, the idea being to affix **multiple** instances of the target species to so as to detect a signal from that particular species," D.I. 42, Ex. 2 at 17-18, 65 (emphasis added) (JA 106-07, 154); *see also id.*, Ex. 5 at 46, 48 (JA-70-72), as depicted in the illustration below.

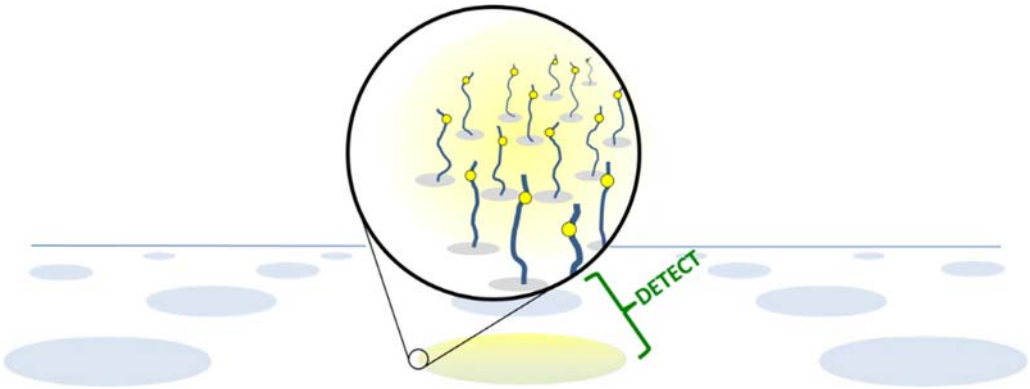


Figure 2: *Detecting a signal from multiple molecules.*

In other words, the alleged prior art disclosed detecting a signal from an ensemble of identical molecules in a spot, rather than detecting a signal from a single molecule.

As the "Summary" of the '441 patent explains: "The present invention provides a bioassay system including a plurality of optical detection apparatuses, and methods of using the bioassay system for nucleic acid detection, e.g., sequencing." '441 patent at 2:10-13. "The bioassay system provided by the invention is capable of large-scale parallel sequencing reactions, i.e., simultaneously sequencing a large number of different nucleic acid templates. Each sequencing reaction uses a single molecule as the template (i.e., single molecule sequencing)." *Id.* at 2:13-18.

The '441 patent emphasizes that each of its devices can sense a signal emitted by a single molecule, *see, e.g.*, *id.* at 3:59-61 ("[e]ach optical detection apparatus may sense the existence of a fluorophore on [a] single molecule by detecting photons emitted from the fluorophore"), and consequently that "[e]ach optical detection apparatus [according to the invention] may be operated independently to detect and identify a single biomolecule affixed thereto." *Id.* at 4:2-4.

This allows for sequencing "nucleic acids without the need for expensive, complicated, and error-prone scanning and analysis systems, e.g., a moving scanning lens or a moving device stage and subsequent image analysis, thus reducing errors and costs." *Id* at 7:34-40. "The bioassay system can detect light signals with substantially improved signal strength, which makes single molecule analysis possible." *Id.* at 7:40-42.

(ii) The preamble of claim 1 is limiting.

"[A] preamble limits the invention if it recites essential structure or steps, or if it is 'necessary to give life, meaning, and vitality' to the claim." *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002). Furthermore, "when reciting additional structure or steps underscored as important by the specification, the preamble may operate as a claim limitation." *Id*.

a) The preamble is limiting because it provides antecedent basis for a term in the bodies of the claims.

"[T]he preamble constitutes a limitation when the claim(s) depend on it for antecedent basis, or when it 'is essential to understand limitations or terms in the claim body.'" *CW Zumbiel Co., Inc. v. Kappos*, 702 F. 3d 1371, 1385 (Fed. Cir. 2012) (*quoting Catalina Mktg.*, 289 F.3d at 808); *Catalina Mktg.*, 289 F.3d at 808 ("[W]hen the preamble is essential to understand limitations or terms in the claim body, the preamble limits claim scope."). In other words, "a preamble phrase that provides antecedent basis for a claim limitation generally limits the scope of the claim." *Deere & Co. v. Bush Hog, LLC*, 703 F. 3d 1349, 1358 (Fed. Cir. 2012).

The preamble of claim 1 is "[a]n apparatus for identifying ***a single biomolecule.***" '441 patent at 26:11 (claim 1).[3] The body of claim 1 correspondingly describes a linker site "treated to

[3] All emphasis in quotations is added unless otherwise noted.

affix ***the biomolecule*** to the linker site." *Id.* at 26:14-15 (claim 1). Asserted dependent claim 9, which depends from claim 1, also refers back to the "single biomolecule" of the preamble. *See, e.g., id.* at 26:35-37 (reciting a light detector that collects light from "the biomolecule"). Thus, as the PTAB determined, IPR2020-01200, Paper 31 at 17 (Final Written Decision), the recitation of "a single biomolecule" in each preamble of the claims provides antecedent basis for one or more references to "the biomolecule" in the bodies of the claims, informing the person of ordinary skill in the art that the linker site of claim 1 is treated to affix a ***single*** biomolecule, and that the detector of claim 9 collects light from a ***single*** biomolecule.[4]

b) The preamble is limiting because it recites a fundamental characteristic of the invention.

The preamble of claim 1 would be limiting even if it did not provide antecedent basis for terms in the bodies of the claims because it describes an apparatus structured to identify a ***single*** biomolecule—a fundamental characteristic of the invention.

"In considering whether a preamble limits a claim, the preamble is analyzed to ascertain whether it states a necessary and defining aspect of the invention, or is simply an introduction to the general field of the claim." *On Demand Machine Corp. v. Ingram Indus., Inc.*, 442 F.3d 1331, 1343 (Fed. Cir. 2006). "[T]he preamble may be construed as limiting when it recites particular structure or steps that are highlighted as important by the specification." *Proveris Sci. Corp. v. Innovasystems, Inc.*, 739 F.3d 1367, 1372 (Fed. Cir. 2014); *Catalina Mktg.*, 289 F.3d at 808

[4] For purposes of claim construction, PGI submits that a person of ordinary skill in the art pertaining to the '441 patent would have had at least a Bachelor of Arts or Bachelor of Science degree in biology, biochemistry, applied physics, or a similar degree, along with at least 1-2 years of experience in the field of optics and sensors, consistent with the definition applied by the PTAB in IPR2020-01200. Personal Genomics continues to believe that the person having ordinary skill in the art also would have had 1-2 years of experience in the field of molecular sequencing, including handling and sequencing nucleic acids, but the PTAB did not agree.

("[W]hen reciting additional structure or steps underscored as important by the specification, the preamble may operate as a claim limitation.").

"Whether to treat a preamble as a limitation is a determination 'resolved only on review of the entire[] . . . patent to gain an understanding of what the inventors actually invented and intended to encompass by the claim.'" *Catalina Mktg.*, 289 F.3d at 808 (*quoting Corning Glass Works v. Sumitomo Elec. USA, Inc.*, 868 F.2d 1251, 1257 (Fed. Cir. 1989)) (alterations in original).

In *On Demand*, the litigants disputed whether "the preamble phrase 'high speed manufacture of a single copy of a book'" required that only one copy of the book be printed. *On Demand*, 442 F.3d at 1343. The district court ruled that "[t]he preamble [] does not limit the claim to the manufacture of a 'single copy' of a book." *Id*. The Federal Circuit reversed on appeal, finding that "[t]he preamble serves to focus the reader on the invention that is being claimed." *Id*. The Federal Circuit explained "that the preamble in this case necessarily limits the claims, in that it states the framework of the invention, whose purpose is rapid single-copy printing of a customer's selected book." *Id*. The court further explained that "[t]he high speed manufacture of a single copy is fundamental to the [patentee's] invention" and ruled that "[t]he district court's [jury] instruction that the preamble in this case does not limit the claim was incorrect, for the entirety of the claim implements the preamble's high speed manufacture of a single copy" of a book. *Id*. at 1344.

Like the specification in *On Demand*, which described the high speed manufacture of a single copy of a book as fundamental to the patentee's invention, the specification of the '441 patent describes identifying a single biomolecule as fundamental to the invention. Indeed, the specification of the '441 patent repeatedly indicates that identifying a single biomolecule, as distinguished from analyzing an ensemble of multiple molecules, is important and fundamental.

For example, the "Background" section of the patent repeatedly indicates that identifying a single biomolecule, as distinguished from deriving information from clusters of molecules, is important and fundamental. The '441 patent observes, for example, that "the US National Institutes of Health (NIH) National Human Genome Research Institute (NHGRI) set a benchmark of reducing per-genome sequencing costs from ten million to approximately one thousand U.S. dollars," '441 patent at 1:41-44, but that "existing sequencing methods require complicated and error-prone image acquisition and analysis steps." *Id.* at 1:48-49. Examples of the complications involved in existing methods include "the known difficulty of asynchrony in both the amplification (e.g., drift between the sequences of ideally clonal templates) and sequencing (e.g., dephasing of stepwise sequencing reactions amongst the sequencing templates) steps of ***clustered sequencing methods***." *Id.* at 1:67-2:6 (emphasis added). "To approach the '$1000 genome' paradigm," the '441 patent states that "devices should be capable of ***sequencing single molecules***," as opposed to only being capable of sequencing clusters of molecules. *See id.* (emphasis added).

The first paragraph of the Summary of the invention states that "[t]he bioassay system provided by the invention is capable of large-scale parallel sequencing reactions, i.e., simultaneously sequencing a large number of different nucleic acid templates," where "[e]ach sequencing reaction uses a single molecule as the template (i.e., single molecule sequencing)." '441 patent at 2:13-18. The Summary goes on to describe "a bioassay system for identifying a single biomolecule at a detecting unit." *Id.* at 2:30-31. Even in instances where an attribute of an invention is not expressly recited in the claim, "[t]he fact that the Summary of the Invention gives primacy" to the attribute "strongly indicates" that the invention requires that attribute. *See Virnetx, Inc. v. Cisco Sys., Inc.*, 767 F.3d 1308, 1318 (Fed. Cir. 2014); *see also C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 864 (Fed. Cir. 2004) (statements in the Summary of the Invention

section are "more likely to support a limiting definition of a claim term"). Here, of course, claim 1 expressly recites an apparatus for identifying "a single biomolecule."

Consistent with the Background and Summary sections of the '441 patent, the "Detailed Description" of the '441 patent repeatedly emphasizes the single-molecule nature of the invention. For example, the Detailed Description states that "[t]he bioassay system consistent with the present invention can be used to monitor a large number . . . of single biomolecules in parallel," *id.* at 3:55-57, and "[f]or all sequencing modalities, the present invention offers the advantage of being able to resequence single molecules." *Id.* at 12:53-54; *see also, e.g., id.* at 3:59-61 ("[e]ach optical detection apparatus may sense the existence of a fluorophore on [a] single molecule by detecting photons emitted from the fluorophore"); *id.* at 4:2-5 ("[e]ach optical detection apparatus . . . may be operated independently to detect and identify a single biomolecule affixed [to a substrate]").

Similarly, all of the apparatuses in the figures of the '441 patent are expressly identified as structures for identifying a single biomolecule. *See, e.g. id.* at Figure 1, 4:2-4 ("Each optical detection apparatus 20 [depicted in Figure 1] may be operated independently to detect and identify a single biomolecule affixed thereto."), Figure 2, 4:52-53 (describing Figure 2 as a "section view" of an apparatus as in Figure 1), 5:49-50 (noting that the "linker site 220 [of Figure 2] may be treated to affix a single biomolecule 30 thereto"), Figure 3, 6:5-6 (noting that the linker site in Figure 3 may be formed in a pinhole "to bind with a biomolecule"), Figure 4, 6:30-31 (describing Figure 4 as a "section view" of an apparatus as in Figure 1), Figures 5-7 (depicting a single nucleic acid 32 affixed to a linker site).

The "Examples" listed in the patent confirm the importance to the invention of identifying single biomolecules. Examples 5 and 6, for example, describe sequencing reactions in which fluorescent signal from a nucleotide within a single nucleic acid is detected by an apparatus

according to the invention at each step. *See id.* at 24:14-26:3. In fact, all of the "Examples" describe apparatuses for detecting a single biomolecule and methods for making and using them, including for sequencing a nucleic acid. *See id.* at 19:25-21:3 (describing in Example 1 "Construction of a High Throughput Bioassay System"); *id.* at 21:5-27 (describing in Example 2 "Attachment and Detection of Biomolecules with High Throughput Bioassay System"); *id.* at 21:30-23:2 (describing in Example 3 "Linking Quantum Dot to Polymerase" to produce an arrangement that the '441 patent describes at 17:57-18:15 as useful for exciting an acceptor chromophore on a nucleotide being polymerized on, or ligated to, a sample nucleic acid); *id.* at 23:4-24:9 (describing in Example 4 "Linking Polymerase to the Device"); *id.* at 24:10-25:30 (describing in Example 5 "Base Extension Sequencing Modalities"); and *id.* at 25:31-26:3 (describing in Example 6 "Sequencing of a Known Nucleic Acid").

The specification is elsewhere replete with references to the use of the invention to identify a single molecule, even if other molecules are involved in the chemistry that enables detection—as in the synthesis of an "end link primer" "on the nucleic acid to be detected," *id.* at 9:53-59, or as in the use of an "intervening molecule" such as a DNA polymerase to attach the single molecule to be detected to the linker site. *See, e.g.*, *id.* at 11:7-16 (explaining that "[i]n some embodiments, the sample nucleic acid may be affixed directly to a linker site by covalent linkage, e.g., disulfide, thioester, amide, phosphodiester, or ester linkages; or by non-covalent linkage, e.g, antibody/antigen or biotin/avidin binding," and "[i]n some embodiments, the sample nucleic acid may be affixed to a linker site by an intervening molecule. In some embodiments, the intervening molecule may be a polymerase, e.g., a DNA polymerase."). Regardless of differences in the underlying chemistry, the configurations of the systems of the '441 patent allow them to "detect

light signals with substantially improved signal strength, which makes single molecule analysis possible." *Id.* at 7:34-42.

Asserted independent claim 16 (from which asserted claims 17-22, 24, 27, and 29 depend) further confirms the importance of single-molecule sequencing to the invention. Claim 16 recites:

> 16. A method of sequencing a nucleic acid, comprising the steps of:
> affixing **one nucleic acid molecule** to the linker site of the apparatus of claim 1;
> and performing nucleic acid sequencing of **the nucleic acid molecule** on the apparatus.

This additional reference to affixing one nucleic acid molecule to the linker site of the apparatus of claim 1 highlights the fact that the apparatus of claim 1 is capable of sequencing a single nucleic acid biomolecule.

Because the preamble of claim 1 recites an aspect of the invention that is repeatedly identified in the specification as important and fundamental, it is limiting. *See, e.g.*, *Poly-Am., L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1310 (Fed. Cir. 2004) (finding a preamble reciting "blown-film" limiting where the specification was "replete with references to the invention as a 'blown-film' liner," where "[t]he phrase [was] used repeatedly to describe the preferred embodiments," and where the preamble "blown-film textured liner" was "restated in each of the patent's seven claims," concluding that the preamble "discloses a fundamental characteristic of the claimed invention that is properly construed as a limitation of the claim itself").

(iii) "An apparatus for identifying a single biomolecule" is capable of detecting a signal associated with an individual biomolecule.

As discussed at length in the sections above, the '441 patent repeatedly describes and illustrates, as an important and fundamental aspect of the invention, the ability to detect a signal

associated with an individual biomolecule, as opposed to multiple molecules. *See generally* § III.A(b)(ii)b) above.

The '441 patent also expressly distinguishes an apparatus for identifying a single biomolecule from apparatuses capable of detecting only signals from multiple biomolecules. For example, the specification distinguishes "devices . . . capable of sequencing single molecules" from devices that use "clustered sequencing methods." *Id.* at 1:67-2:1. With clustered sequencing methods, multiple identical copies of a molecule are used together with the same light detector. Such methods encounter difficulties when molecules in the cluster fall out of step during sequencing and are no longer synchronized with other molecules in the cluster. As the specification explains, "devices . . . capable of sequencing single molecules [] avoid the known difficulty of asynchrony" such as "drift between the sequences of ideally clonal templates" or "dephasing of the stepwise sequencing reactions amongst the sequencing templates." *Id.* at 1:67-2:6.

Consequently, a person of ordinary skill in the art would understand that "single" as recited in claim 1 is an exclusive word referring to a count of only one, as understood in plain English. For example, a person who is single is not married. A description of a field with a tree in it leaves open the possibility that the field has multiple trees, but a description of a field with a single tree in it does not. Thus, "[a]n apparatus for identifying a single biomolecule" is capable of detecting a signal associated with an individual biomolecule. An apparatus capable of detecting a signal only from multiple identical biomolecules is not "[a]n apparatus for identifying a single biomolecule." *See also* IPR2020-01200, Ex. 2008 at 9-21 (JA 319-31).

2. Defendant's Answering Position

The preamble of claim 1 recites "[a]n apparatus for identifying a single biomolecule." The parties' dispute with regard to the preamble is two-fold. First, the parties dispute whether collateral estoppel bars PacBio from challenging PGI's proposed construction. Second, as to the substance,

the parties dispute whether the preamble should be narrowly construed so that the claims are limited to systems where the claimed "identifying" can take place by a particular method, specifically, detection of signal from only an "individual biomolecule" (PGI's position) or not (PacBio's position). For the reasons stated below, collateral estoppel does not apply, and the Court should not adopt PGI's narrowing construction.

(a) Collateral Estoppel Does Not Apply

PGI asserts that PacBio is collaterally estopped from challenging PGI's narrowing claim construction because the PTAB allegedly adopted its construction in IPR2020-01200. *See* Joint Brief at 14-19. Yet, PGI is now advancing a construction ***different*** from what it presented to the PTAB and that the PTAB did not adopt. Collateral estoppel thus cannot possibly apply. And, even if PGI were advancing the same construction that was before the PTAB, PGI is incorrect that a PTAB claim construction in a final written decision that has not been subject to appellate review is sufficient to trigger collateral estoppel.

(i) Collateral Estoppel Does Apply Because PGI Is Advancing A New Construction

A threshold requirement for collateral estoppel to apply is that the same issue have been both previously litigated and adjudicated. That is not the case here.

At the PTAB, PGI asserted that the preamble of claim 1, which recites "[a]n apparatus for identifying a single biomolecule," be construed to mean "a structure for identifying an individual biomolecule, as opposed to, for example, multiple copies of a biomolecule in an ensemble." Ex. 21 at 9 (JA 907). The PTAB, for its part, stated that the preamble requires an apparatus "capable of identifying a single biomolecule," further noting that it provided antecedent basis for "the biomolecule," which appears later in the claim. Ex. 1 at 21 (JA 45).

In this Court, however, PGI advances a construction that differs from what it previously proposed in the PTAB. PGI now contends that the preamble should be construed to refer to something that "is capable of detecting a signal associated with an individual biomolecule, as opposed to multiple identical biomolecules." Joint Brief at 13. The three different relevant constructions are shown in the table below:

PGI's Proposed Construction In The PTAB	The PTAB's Construction	PGI's Proposed Construction In This Court
"a structure for identifying an individual biomolecule, as opposed to, for example, multiple copies of a biomolecule in an ensemble"	"we determine that the preamble of claim 1 is limiting, requires an apparatus capable of identifying a single biomolecule, and provides antecedent basis for 'the biomolecule' as used in the body of the independent claims, which should be read as 'the single biomolecule' introduced in the preamble.	the apparatus "is capable of detecting a signal associated with an individual biomolecule, as opposed to multiple identical biomolecules"

Relative to its proposed PTAB construction, PGI's new district court construction introduces the concept of a device that is "capable of" (but perhaps not limited to)[5] "detecting a signal" "associated with" an individual biomolecule. While the PTAB's construction refers to an apparatus that is "capable of identifying a single biomolecule," this "capability" concept was introduced *sua sponte* by the PTAB in its final written decision and is not what PGI proposed. As such, with respect to at least the "capability" aspect of PGI's proposed construction, PacBio has not had a full and fair opportunity to litigate the issue. The PTAB's construction also does not recite a "signal associated with an individual biomolecule." Even to the extent one argues that the PTAB's construction is substantively equivalent to detecting a signal from an "individual biomolecule," the substantial difference in terminology between PGI's proposed construction and what appears in the PTAB's decision counsels against applying collateral estoppel. Likewise, while both PGI's PTAB construction and its new district court construction include a negative limitation, PGI's negative limitation in the district court abandons the concept of "copies" and

[5] It is unclear the extent to which PGI contends the claims encompass systems that detect signal from multiple biomolecules, if at all. Although PGI's proposed construction of the preamble recites that systems should be "capable" of detecting a signal from an "individual biomolecule," it also includes the proviso "as opposed to multiple identical biomolecules," which suggests that PGI intends for its construction to exclude systems that detect signal from an ensemble of molecules. PGI's brief includes several statements further confirming this. *See, e.g.*, Joint Brief at 28 ("Consequently, a person of ordinary skill in the art would understand that 'single' as recited in claim 1 is an exclusive word referring to a count of only one, as understood in plain English."); *id.* (The "'441 patent repeatedly describes and illustrates, as an important and fundamental aspect of the invention, the ability to detect a signal associated with an individual biomolecule, as opposed to multiple molecules."); *id.* at 24 ("For example, the 'Background' section of the patent repeatedly indicates that identifying a single biomolecule, as distinguished from deriving information from clusters of molecules, is important and fundamental."); *id.* at 2 ("Moreover, the specification distinguishes identifying a single biomolecule from detecting signals from multiple biomolecules in a cluster or ensemble."). Whether PGI contends its claims completely exclude any system that detects signal from multiple molecules or encompass such systems so long as they are "capable" of detecting signal from a single biomolecule is irrelevant because, as shown herein, even the latter broader view of the claims is erroneous.

instead just refers to "multiple identical" molecules. The PTAB's construction includes no provisos at all. Thus, in this Court, PGI has completely overhauled its previous PTAB construction, making it broader in some facets and narrower in others.

The key point, however, is that PGI cannot establish that the specific construction it now advances was actually litigated in the IPRs. Because PacBio has not had "a full and fair opportunity to litigate the issues" raised by PGI's new claim construction, collateral estoppel does not apply. *See Jet, Inc. v. Sewage Aeration Sys.*, 223 F.3d 1360, 1365-66 (Fed. Cir. 2000); *see also UCP Int'l Co. Ltd. v. Balsam Brands Inc.*, 787 Fed. Appx. 691, 706 (Fed. Cir. 2019) ("Because the direct connection requirement was added to the construction of 'pivot joint' at summary judgment, collateral estoppel—assuming without deciding that it applies to the Frontgate Order—does not preclude Balsam from challenging that new requirement."); *In re Koninklijke Philips Pat. Litig.*, No. 18-cv-01885-HSG, 2020 WL 2733931, at *1 (N.D. Cal. May 26, 2020) ("There is also no evidence that the court addressed constructions for 'identifying,' 'determining,' and 'retrieving.' Accordingly, the claim construction issues were not actually addressed and decided by the Federal Circuit and the Court is not bound by the underlying PTAB interpretations.").

(ii) Even If PGI Were Pursuing The Same Construction It Pursued In The PTAB, Collateral Estoppel Still Would Not Apply

Collateral estoppel does not apply for the simple reason that the PGI is advancing a construction different from what it previously advanced before the PTAB and that the PTAB never adopted. Yet, even if the exact claim construction that was at issue before the PTAB were at issue here, collateral estoppel still would not apply because it is unsupported in law. Judge Stark, formerly of this Court, previously rejected the argument that a PTAB claim construction that has not yet been affirmed on appeal has preclusive effect, noting that "this Court is unaware of any binding caselaw holding that a PTAB claim construction ruling has preclusive effect in district

court prior to its review by the Federal Circuit." *See Becton, Dickinson & Co. v. Neumodx Molecular, Inc.*, No. 19-1126-LPS, 2021 WL 1854650, at *3 n.2 (D. Del. May 10, 2021).

In fact, Federal Circuit law only become "final" for purposes of preclusion when they are affirmed on appeal (or if the appeal is dismissed or none is filed). For example, in *MaxLinear*, the Federal Circuit considered a patent that was the subject of three IPRs. *MaxLinear, Inc. v. CF CRESPE LLC*, 880 F.3d 1373, 1375 (Fed. Cir. 2018). The first two IPR determinations were affirmed while appeal of the third was pending. *Id.* at 1376-77. In considering the third IPR, the Federal Circuit explained that the earlier IPRs were "affirmed by our court during the pendency of this appeal" and so "became final while this case was pending on appeal." *Id.* at 1374, 1376. The Federal Circuit likewise stated that "the precluding judgment..c[ame] into existence while the case as to which preclusion is sought (this case) is on appeal." *Id.* at 1376-77 (noting that the "preclusive effect of the prior adjudications, and subsequent affirmations, has finally resolved the issue..."); *see also XY, LLC v. Trans Ova Genetics, L.C.*, 890 F.3d 1282, 1294 (Fed. Cir. 2018) (Federal Circuit affirmance of an IPR decision "renders final a judgment...and has an immediate issue-preclusive effect"); *Papst Licensing GmbH & Co. KG v. Samsung Elecs. Am., Inc.*, 924 F.3d 1243, 1249 (Fed. Cir. 2019) (once "Papst voluntarily dismissed its appeals from [the IPR decisions]...[t]hose decisions therefore became final").

Consistent with the Federal Circuit cases, there is clear evidence of Congressional intent that PTAB decisions are subject to Federal Circuit oversight and should have no preclusive effect unless and until reviewed. In the context of IPRs, 35 U.S.C. §§ 319 and 141(c) provide an exclusive right of appeal to the Federal Circuit. On the other hand, 35 U.S.C. § 315 provides for a specific form of estoppel upon "a final written decision" as provided for in 35 U.S.C. § 315(e)(1)-(2). Nothing in these statutes mentions PTAB claim construction determinations. Issue preclusion

should not apply "when a statutory purpose to the contrary is evident," as is the case here. *B&B Hardware, Inc. v. Hargis Industries, Inc.*, 575 U.S. 138, 148 (2015).

PGI cites to *SynQor* for its collateral estoppel position. But that case does not help PGI. *See, e.g.*, *SynQor, Inc. v. Vicor Corp.*, 988 F.3d 1341, 1346 n.1 (Fed. Cir. 2021) (noting that Plaintiff could not have raised issue preclusion earlier because the final decision in two related reexaminations had not yet become "final," i.e. reviewed by the Federal Circuit, until after the PTAB had issued its judgement in the third IPR proceeding). None of the law PGI cites applies collateral estoppel to a claim construction ruling in an IPR proceeding that is still under review by the Federal Circuit. Instead, PGI relies on cases where the courts applied collateral estoppel based on ***another district court's*** decision. Joint Brief at 17-19. Because PGI cites no authority establishing that a PTAB claim construction decision that has not been reviewed on appeal triggers collateral estoppel, the Court should not apply collateral estoppel here, but should instead decide the issue on the merits.

(b) The Preamble Encompasses Detection Of Signal From Multiple Molecules

In its brief, PGI tellingly advances no meaningful argument that the claim language supports its construction. Just the opposite, PGI runs from the claim language, drastically rewriting it to introduce new limitations so that the claims only encompass devices capable of detecting "signal" from an "individual biomolecule." As documented below, however, the independent claims and dependent claims mutually confirm that no such construction is warranted. The specification echoes this, expressly teaching that the claimed invention should be used with technologies based on the detection of signal from multiple molecules. PGI's proposed construction reflects nothing more than an improper attempt to limit the claims to preferred embodiments and should be rejected.

(i) The Preamble's Broad Language Covers Detection Of Signal From Multiple Molecules

Claim 1 recites "[a]n apparatus for identifying a single biomolecule," and the other independent claims of the '441 patent include the same language. While PGI contends that the preamble should be construed to require that the apparatus be "capable" of detecting a "signal" from only an "individual biomolecule," the claim does not say this at all. The claim language merely states "identifying a single biomolecule," placing no limitations on ***how*** the identification is done. The term "identifying" has a plain and ordinary meaning, which is simply to determine what something is. The very dictionaries that PGI relied upon in the IPR confirm this. *See, e.g.*, Ex. 9 ("establish or indicate who or what (someone or something) is") (JA 527-32); Ex. 10 ("establish the identity") (JA 534-537). PGI's own expert in the IPR likewise agreed that to "identify" simply means "to determine the identity of in a broad sense." *See* Ex. 6 at 93:2-8 (JA 422).

Importantly, "identifying" a single molecule does not require detecting a signal from just a single, individual molecule. It can be done other ways. Specifically, one can determine what a molecule is by first copying it and then analyzing the signal from the collection of identical molecules. As documented above, this is precisely what was described in the prior art Shendure reference and Illumina technology, which was well-known before the '441 patent's 2007 priority date. *See* Joint Brief at 5-7.

PGI's proposed construction is an implicit admission that the preamble—as drafted—is not, in fact, limited to systems capable of detecting signal from a single molecule but rather broadly covers identifying a single biomolecule based on a signal from a collection of individual biomolecules. Indeed, PGI argues that the preamble should be construed to refer to an apparatus that "is capable of detecting a signal associated with an individual biomolecule, as opposed to

multiple identical biomolecules." PGI's wholesale introduction of the language "signal associated with an individual biomolecule" drastically alters the claim language and, as shown further below, is nothing more than an attempt to limit the claims to preferred embodiments. *See* Joint Brief at 45-48. Likewise, inclusion of the negative limitation excluding certain well-known molecular identification techniques demonstrates that the broad language "identifying a single biomolecule" otherwise encompasses determining the identity of a single biomolecule from a collection of multiple identical biomolecules. If this were not so, PGI would not be proposing a narrowing construction with a negative limitation to specifically exclude such techniques.

(ii) The Dependent Claims Confirm That Claim 1 Is Intended To Cover Detecting Signal From Multiple Molecules

While the language of the preamble as drafted confirms that PGI's construction is erroneous, the dependent claims remove all doubt that the claims encompass detection of signal from multiple biomolecules. Both claims 26 and 30 include limitations establishing that the claims necessarily encompass detection of signal from multiple biomolecules. Tellingly, PGI addresses neither of these claims in its opening brief.

a) Dependent Claim 26 Recites That The Biomolecule Is "Amplified At The Linker Site"

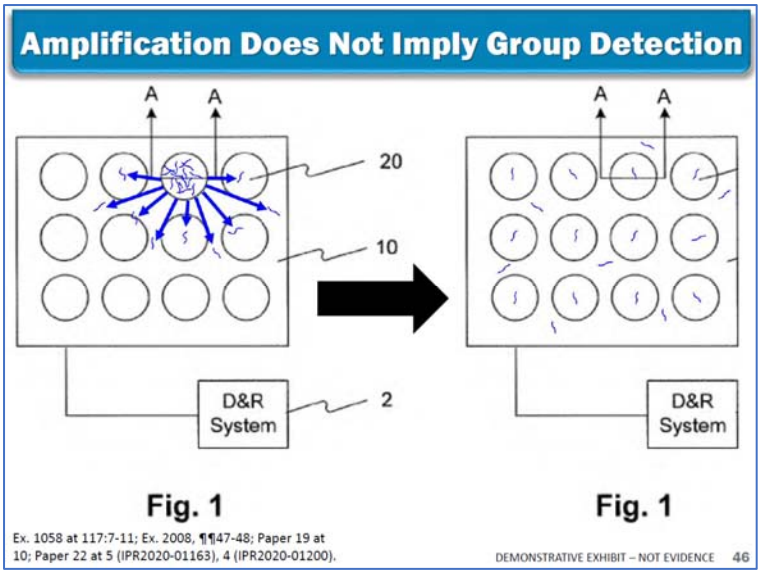
Claim 26 depends from claim 16, which refers back to independent claim 1:

> 16. A method of sequencing a nucleic acid, comprising the steps of:
> affixing one nucleic acid molecule to the linker site of the apparatus of claim 1; and
> performing nucleic acid sequencing of the nucleic acid molecule on the apparatus.
>
> 26. The method of claim 16, wherein the nucleic acid is amplified at the linker site before nucleic acid sequencing.

'441 patent at claims 16, 26. Claim 26 requires that the nucleic acid is first "amplified at the linker site" before sequencing—*i.e.*, that multiple copies of the same identical molecule are created. *See*

D.I. 42-6 ¶ 48 (PGI's IPR expert agreeing that claim 26 refers to generating "multiple copies of a molecule") (JA 327). Contrary to PGI's position in its brief that the word "single" in the preamble is "an exclusive word referring to a count of only one," the language "identifying a single biomolecule" in the preamble of claim 1 must encompass a process by which a signal is detected from multiple identical molecules. *See, e.g.*, *Littelfuse, Inc. v. Mersen USA EP Corp.*, 29 F.4th 1376, 1380 (2022) ("By definition, an independent claim is broader than a claim that depends from it, so if a dependent claim reads on a particular embodiment of the claimed invention, the corresponding independent claim must cover that embodiment as well."). This is critical because there is no additional language anywhere in the preamble (or anywhere else in the claim) that could serve to justify requiring the "capability" of detecting a signal from an "individual biomolecule."

PGI has never had a credible explanation for claim 26. In the IPR, PGI sought to exclude from the scope of the claims any identification technique that involved detecting signal from multiple molecules and did not present the "capability" construction it now presents. To that end, PGI presented a made-up theory of what claim 26 supposedly encompasses, which its own expert undermined as "speculative." PGI relied on its expert, Dr. Harris, who opined that claim 26 may refer to generating multiple copies of a DNA molecule "in the vicinity" of the linker site "en route to attaching one copy of the molecule to each of [the] multiple different apparatuses on the same bioassay substrate...." D.I. 42-6 ¶ 48 (JA 327). PGI provided the following demonstrative to illustrate this:



Ex. 11 at 46 (JA 540).

On the left is an apparatus that supposedly corresponds to the alleged invention, where each of the circles is intended to be one of the claimed "linker sites." PGI's idea was that claim 26 refers to an approach where some location "in the vicinity" of a linker site acts as a central site for making copies of the molecule of interest (shown as light blue squiggles). Then, as shown on the right, individual molecules somehow drift off to the linker sites so that there is only a single molecule at each linker site and there would then only be detection of signal from an individual biomolecule. *See* Ex. 18 at 48:9-14 (JA 747). This theory is not just contrary to the claim language, but also pure nonsense.

On cross-examination, PGI's expert testified that it was "speculative" and not a "strategy that was in the mind of the people who wrote the '441 patent:"

> Q. Okay. What do you mean when you say "en route to attaching one copy of the molecule to each of multiple different apparatuses on the same bioassay substrate"?
>
> A. Well, this is speculative and so I can't assert that '441 had this intent because they didn't describe how they were going to take advantage of the amplification process.

> But one can imagine that if you had a dilute sample of nucleic acid targets and that you wanted to have replicate tries at each of those dilute samples in order to get good statistical data, that you would invent a strategy whereby you could replicate on the substrate either at or attached to it multiple copies and those multiple copies could diffuse across the apparatus to other attachment linker sites and those linker sites might then attach the amplified molecules.
>
> It's speculative and I would not assert that this is a strategy that was in the mind of the people who wrote the '441 patent. It is a possible reason why you would want to generate multiple copies in the vicinity of a linker site.

Ex. 6 at 118:12-119:9 (JA 429). Far from suggesting that PGI's interpretation of the claims was a reasonable description of what had been invented, Dr. Harris described it as reflecting an approach that "one can imagine" and that one would have to "invent" anew.

b) Dependent Claim 30 Recites Affixing "One or More" Biomolecules To The Linker Site

Dependent claim 30, like claim 26, depends from claim 1 and reads as follows:

> 30. A method of detecting a biomolecule, comprising the steps of:
> affixing one or more biomolecule to the linker site of the apparatus of claim 1; and
> detecting the biomolecule on the apparatus.

'441 patent at claim 30. Referring to affixing "***one or more***" biomolecules to the linker site, claim 30 unambiguously contemplates detecting signal from multiple molecules. If there is more than one molecule at the linker site from which the signal emanates, the claims must necessarily encompass detection of signal from multiple molecules. Thus just like claim 26, claim 30 establishes that the preamble language "identifying a single biomolecule" covers detection of signal from multiple biomolecules. Again, nothing in this language (or any other claim language) could serve as the source of a narrowing limitation to require that the claimed systems be "capable" of detecting signal from an "individual biomolecule."

Just the opposite, the language of claim 30 also demonstrates that the claims of the '441 patent use the term "biomolecule" to refer to a ***species*** of molecule and not just a single, individual

molecule. Claim 30 recites to "affixing one ***or more*** biomolecule," which provides an antecedent basis for the subsequent claim language that requires "detecting ***the*** biomolecule." Use of the singular form "the biomolecule" to refer to "one or more biomolecule" shows that the term "biomolecule" refers to the species of biomolecule, not to a singular biomolecule. If that were not true, the language "one ***or more***" that explicitly contemplates ***multiple*** identical biomolecules would have no meaning. "A claim construction that gives meaning to all the terms of the claim is preferred over one that does not do so." *Power Mosfet Techs., LLC v. Siemens AG*, 378 F.3d 1396, 1409-10 (Fed. Cir. 2004).

As with claim 26, PGI has never had a persuasive response to claim 30. In the IPR, where PGI was seeking to fully exclude from the claims any techniques that involved detection of signal from multiple molecules, PGI pointed to its expert, who opined that claim 30 refers to affixing two "biomolecules" of different type and function at the linker site, and then only detecting signal from one of them. *See* Ex. 11 at 49 (JA 541); Ex. 21 at 11 (JA 909); D.I. 42-6 ¶ 52 (JA 329). Dr. Harris posits the scenario of attaching a nucleic acid to a linker site indirectly via a polymerase enzyme. In Dr. Harris's scenario, two kinds of alleged "biomolecule" are attached to the linker site (i.e., the nucleic acid and polymerase). But only the nucleic acid is detected, while the polymerase is just a passive connector. D.I. 42-6 ¶ 52 (JA 329); Ex. 11 at 49 (JA 541). This explanation is without merit.

In the claims, the "biomolecule" is the thing that is "identified" or "detected." *See, e.g.*, '441 patent at claim 1 ("An apparatus for identifying a single biomolecule…."); *id.* at claim 9 ("wherein the light detector collects light from the biomolecule"); *id.* at claim 30 ("A method of detecting a biomolecule…."). Nowhere do the claims suggest that the "biomolecule" is a passive

entity that is not the subject of identification, such as a molecule that is merely used as an intermediate to attach the "biomolecule" to the linker site.

When the claims wish to refer to a molecule that serves this intermediate linking function, it uses a term different from "biomolecule." Specifically, it uses the term "linking molecule," as appears in dependent claim 34, which depends from claim 30. *See id.* at claim 34 ("34. The method of claim 33, wherein the biomolecule is affixed to the linker site of the apparatus by a linking molecule."). PGI's attempt to explain away claim 30 by saying an undetected "linking molecule" can be the "biomolecule" that is the subject of detection is without merit.

Again, as PGI's own expert acknowledged, the claims distinguish the two concepts:

Q. Okay. Now, what is a linking molecule?
A. I think it's self-evident. A molecule that connects two things together.
Q. The linking molecule in the claims is different from the biomolecule that's detected; correct?
A. In this case, it would – it would – they are making that distinction.
Q. Okay. One example that the patent provides of a linking molecule is a DNA polymerase; correct?
A. I believe that they use that expression to describe the polymerase.

Ex. 6 at 108:2-13 (JA 426). If the term biomolecule included molecules that performed a linking function, there would be no need to separately refer to a "linking molecule" in claim 34. *See Power Mosfet*, 378 F.3d at 1409-10.

(iii) The Specification Confirms That The Claims Encompass Detection Of Signal From Multiple Molecules

While the claim language alone establishes that PGI's "individual biomolecule" construction is erroneous, the specification confirms this by disclosing DNA sequencing embodiments based on well-known approaches where signal is detected from multiple biomolecules. *See* Joint Brief at 5-7. The specification is express that these approaches may be

used with the "invention." PGI, for its part, relies on inapposite cases and otherwise identifies nothing in the specification—let alone a clear disavowal or disclaimer—to justify excluding such embodiments from the scope of the claims or even limiting the claims to systems that are "capable" of detecting a signal from an "individual biomolecule."

a) The '441 Patent Discloses Embodiments Based On Detection Of Signal From Multiple Molecules

PGI asserts that the '441 patent "expressly distinguishes an apparatus for identifying a single biomolecule from apparatuses capable of detecting only signals from multiple biomolecules," such as "clustered sequencing methods," where "multiple identical copies of a molecule are used together with the same light detector." Joint Brief at 28. This is simply wrong. As noted above, the '441 patent ***claims*** precisely this in claim 26, and as set forth below, expressly discloses that such "clustered" approaches should be used with the alleged invention.

The specification expressly describes "Sequencing Modalities" that can be used either with the claimed "invention" or in "some embodiments," identifying at least three references that set forth such approaches, including U.S. Patent No. 6,946,249 ("the '249 patent"), Shendure, and U.S. Patent No. 5,302,509 ("Cheeseman"):

- "The bioassay system provided by the ***present invention*** can be used to detect and sequence nucleic acids by means known in the art, as reviewed in, e.g., U.S. Pat. No. 6,946,249 and Shendure et al., *Nat. Rev. Genet.* 5:335-44 (2004)." '441 patent at 12:37-40.

- "In ***some embodiments***, the light detection apparatuses provided by the invention can be used to perform base extension sequencing as disclosed in, e.g., U.S. Pat. No. 5,302,509." *Id.* at 13:2-4.

The references cited in these passages are incorporated by reference into the '441 patent "for all purposes as well as for the proposition that is recited." *Id.* at 18:51-54. Each of these references teaches an approach based on detection of signal from multiple molecules.

As noted above, the Shendure article describes methods where the "uniting feature" is the use of "isolated (that is, clonal) amplification," after which "each feature to be sequenced contains thousands to millions of copies of an identical DNA molecule[.]" Ex. 7 at 340 (JA 512). As the Shendure reference explains, "the amplification is necessary to achieve sufficient signal for detection." Thus, in Shendure, the identification takes place by detection of signal from multiple molecules, a point PGI's expert confirmed:

> Q. So this section of the Shendure Exhibit No. 1053 entitled "Cyclic-Array Sequencing on Amplified Molecules" is describing sequencing approaches where signal is detected for multiple molecules of the same species; correct?
>
> A. That is correct.

See Ex. 6 at 86:16-21 (JA 421).

The '249 patent, like Shendure, also discloses sequencing techniques that involve detecting a signal from multiple molecules of the same species. For example, the '249 patent discloses an approach cited in U.S. Patent No. 5,002,867 to Macevicz in which there are "copies of the target sequence" anchored to a solid support. Ex. 12 at 9:39-66 (JA 551). Dr. Harris confirmed that this was an approach that was "[c]learly multiple molecules of the same species." Ex. 6 at 78:11-80:10 (JA 419).

As to the second disclosure, the '441 patent cites to U.S. Patent No. 5,302,509 to Cheeseman. The Cheeseman reference explains that the "purpose of the present invention is to determine the sequence of a set of identical single stranded DNA molecules, therefore it will be assumed that such strands are initially provided." Ex. 13 at 3:14-17 (JA 571). As PGI's expert confirmed, Cheeseman is another example of a reference in which the sequencing is based on detecting a signal for multiple molecules of the same species:

> Q. Okay. And we discussed earlier the Cheeseman reference is a reference in which the sequencing is based on detecting a signal for multiple molecules of the same species; correct?
>
> A. That is correct.

Ex. 6 at 88:12-17 (JA 421). Dr. Harris could not have been clearer that "Cheeseman is ***intimately*** about detecting many molecules." *Id.* at 226:24-25 (JA 456).

As these three references demonstrate, the '441 patent's specification expressly teaches "Sequencing Modalities" wherein the identity of a biomolecule is determined by detecting a signal from multiple biomolecules. The fact that the '441 patent discloses at least three such references drives home the inventors' intent for their alleged invention to cover approaches based on detecting signal from multiple molecules, not to impose some sort of requirement that claimed systems also have another mode of operation so that they are "capable" of detecting an "individual biomolecule." Notably, the patent teaches that Cheeseman, Shendure, and the '249 patent are incorporated by reference "for the proposition that is recited." '441 patent at 18:53-54. That recited proposition was that the techniques in those references—which are based on detection of signal from multiple copies of a molecule and do not detect signal from individual biomolecules—may be used with the alleged invention of the '441 patent. The public was entitled to take the patentee at its word.

It is unsurprising that the patentees included such disclosure in their specification because, as PGI's expert also confirmed, at the relevant timeframe DNA sequencing technology based on this approach was "commercially important and scientifically important" and discussed at "virtually every conference." *See* Ex. 6 at 34:15-35:9, 35:19-24 (JA 408). Regardless, to the extent PGI seeks to construe claim 1's preamble in a manner that would exclude these embodiments, this construction should be rejected. *See Oatey Co. v. IPS Corp.*, 514 F.3d 1271,

1276 (Fed. Cir. 2008) ("We normally do not interpret claim terms in a way that excludes embodiments disclosed in the specification") (citations omitted).

b) Detecting Signal From A "Single Biomolecule" Is Not A "Fundamental Characteristic" Of The Alleged Invention

PGI argues that its construction should be adopted because the specification teaches that "identifying a single biomolecule" is a "fundamental characteristic of the invention." Joint Brief at 1, 23. Yet, as shown above, merely "identifying a single biomolecule" does not require detection of a signal from an "individual biomolecule." *See* Joint Brief at 35-36.

Unable to rely upon the claim language as drafted, PGI cites various portions of the specification that allegedly "repeatedly indicate[] that identifying a signal biomolecule, as distinguished from analyzing an ensemble of multiple molecules, is important and fundamental." Joint Brief at 23-27. None of PGI's examples, however, demonstrate that a "fundamental characteristic" of claim 1 is detecting a signal from a single, individual molecule, as opposed to merely identifying—*i.e.*, determining the identity of—a target biomolecule, whether from one or multiple identical copies of the molecule. Certainly, PGI does not identify anything approaching the disclaimer or disavowal needed to justify its attempt to substantially narrow the claim language beyond its plain and ordinary meaning.

For example, PGI notes that the "Background" of the patent "states that 'devices should be capable of ***sequencing single molecules***,'" because this allegedly avoids an "asynchrony" problem with prior art methods that detected signal from multiple molecules. Joint Brief at 24, 28 (citing '441 patent at 1:67-2:6). Yet, this is at most a potential goal or benefit of the alleged invention, which does not limit claims. The Federal Circuit has been clear that "it is generally not appropriate 'to limit claim language to exclude particular devices because they do not serve a perceived 'purpose' of the invention'" *Praxair, Inc. v. ATMI, Inc.*, 543 F.3d 1306, 1325 (Fed. Cir. 2008).

Likewise, this description in the '441 patent of an alleged benefit of the invention over the prior art does not disavow or disclaim the express teaching in the specification that the "invention" can nonetheless be used in sequencing modalities where signal is detected from multiple molecules. *See Epistar Corp. v. Int'l Trade Comm'n*, 566 F.3d 1321, 1335 (Fed. Cir. 2009) ("A patentee's discussion of the shortcomings of certain techniques is not a disavowal of the use of those techniques in a manner consistent with the claimed invention."); *Ventana Med. Sys., Inc. v. Biogenex Lab'ys, Inc.*, 473 F.3d 1173, 1181 (Fed. Cir. 2006) ("general statements by the inventors indicating that the invention is intended to improve upon prior art … without more, will not be interpreted to disclaim every feature of every prior art device discussed in the 'BACKGROUND ART' section of the patent").

PGI goes on to identify ***examples*** where the specification refers to sequencing reactions using "a single molecule as the template." *See* Joint Brief at 24-25. PGI argues that the '441 patent "repeatedly emphasizes the single-molecule nature of the invention." *Id.* at 25. But, even to the extent the '441 patent includes embodiments or examples that involve detecting a signal from an individual biomolecule, and even to the extent those are preferred embodiments, it would be legal error to limit the claims so that they only encompass systems that have that particular feature of the preferred embodiment and exclude from the scope of the claims systems that do not. It is black letter law that "claims are not necessarily and not usually limited in scope simply to the preferred embodiment." *Akamai Techs., Inc. v. Limelight Networks, Inc.*, 805 F.3d 1368, 1375 (Fed. Cir. 2015) (quoting *RF Del. v. Pac. Keystone Techs., Inc.*, 326 F.3d 1255, 1263 (Fed. Cir. 2003)). Claims should only be limited "1) when a patentee sets out a definition and acts as his own lexicographer, or 2) when the patentee disavows the full scope of a claim term either in the specification or during prosecution." *Apple Inc. v. MPH Techs. Oy*, 28 F.4th 254, 259 (Fed. Cir.

2022)(citation omitted). PGI does not even attempt to identify any disavowal, disclaimer, or lexicography in the specification that would justify this. Here, it would be particularly inappropriate for the Board to limit the claims to embodiments because the specifications instructs not to do so:

> It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only, and are not restrictive of the claimed invention.

'441 patent at 3:14-17; *see also id.* at 18:59-61 ("The embodiments within the specification provide an illustration of embodiments of the invention and should not be construed to limit the scope of the invention.").

PGI cites inapposite cases. PGI relies most heavily on *On Demand Machine Corp. v. Ingram Industries, Inc.*, 442 F.3d 1331, 1343 (Fed. Cir. 2006). There, the parties disputed whether the preamble language "high speed manufacture of a single copy of a book" limited the claims to the manufacture of only a "single book," as the preamble stated, or if it covered mass production of many books. *Id.* The Federal Circuit held that the preamble was limited to a "single book" based on the claim language and the specification, the latter of which only taught manufacture of a single book and had no descriptions to the contrary. Here, however, the claim language as drafted does not support PGI's position, which PGI effectively acknowledges by the fact that its proposed construction alters the claim language wholesale. Unlike the claims of the '441 patent, *On Demand* also did not present dependent claims that called for a broader construction. Likewise, unlike the specification in *On Demand* that uniformly supported a narrow interpretation, the '441 patent

expressly teaches embodiments contrary to PGI's proposed construction where signal is detected from multiple molecules.[6]

(c) The Prosecution History Undermines PGI's Construction

To the extent PGI contends that a "fundamental characteristic" of the alleged invention is detection of a signal from only an "individual biomolecule," this is totally undermined by the original application to which the '441 patent claims priority. The '441 patent claims the benefit of provisional application No. 61/036,652 (the "'652 application"), which is incorporated by reference into the '441 patent. *See* '441 patent at 1:6-11. Just like the '441 patent, the '652 application includes claims that demonstrate the patentees' intent to capture processes that detect a signal from multiple identical biomolecules.

Specifically, claim 2 of the '652 application recites sequencing "plural nucleic acids simultaneously." *See* Ex. 14 at claim 2 (JA 613-14). To accomplish this, the claim recites "plural separate binding sites," wherein the "binding site randomly catches and fixes a nucleic acid to be sequenced on the binding site position." *Id.* Just like claim 26 of the '441 patent, dependent claim 6 of the '652 application recites "wherein a amplification process can be included after said nucleic acid binded to said binding site." *Id*. at claim 6 (JA 615). And just like claim 26 of the '441 patent, the "amplification" takes place at "said" "binding site position" where the nucleic acid is sequenced.

[6] PGI's remaining cases are similarly distinguishable, involving situations where disputed claim terms were used interchangeably with other terms or expressly defined. *See Virnetx, Inc. v. Cisco Sys., Inc.*, 767 F.3d 1308, 1317 (Fed. Cir. 2014) (construing the phrase "secure communication to link" to have attributes of a "VPN" where there were no embodiments to the contrary and the specification used "secure communication link" and "VPN" interchangeably); *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 866 (Fed. Cir. 2004) (finding that the specification expressly defines claim terms, explaining that "the specification demonstrates that Bard clearly defined the terms 'implant' and 'plug' in claim 20 as requiring a pleated surface").

The only sensible interpretation of this claim is that the signal for the DNA sequencing arises from a collection of identical copies of a molecule, just as described in Shendure, Cheeseman, and the '249 patent. PGI's proposed construction requiring signal from only an "individual biomolecule" is directly at odds with the '652 application's disclosure of detecting a signal from multiple identical biomolecules.

(d) The Extrinsic Evidence Establishes That PGI's Construction Was Erroneous

While the intrinsic evidence uniformly establishes that PGI's construction is erroneous, so too does the extrinsic evidence. PGI's IPR expert asserted that usage of the term "single molecule sequencing" in the specification supports its position because "single molecule sequencing" was a "term of art" that refers to "sequencing an individual biomolecule, not multiple copies of a biomolecule together." D.I. 42-6 ¶ 42 (JA 324).

In fact, Dr. Harris is an inventor on a number of DNA sequencing patents from his time at a company called Helicos, some of which he cites in his declaration. *See* D.I. 42-6 ¶¶ 8-11 (JA 312-13). One Helicos patent is U.S. Patent No. 7,169,560 ("the '560 patent"), which was asserted against Illumina in patent infringement litigation. *See* Ex. 15 at 1, 25-27 (JA 622, 646-48). In that litigation, Helicos asserted that the Illumina technology was a "single molecule DNA sequencing" technology, even though, as Dr. Harris confirmed, it undisputedly is based on detecting signal from multiple copies of a molecule. *See* Ex. 6 at 36:7-49:2, 86:16-25 (JA 408-11, 421); Ex. 16 (JA 655-658). Thus, Dr. Harris' own former company asserted in litigation that "single molecule sequencing" encompassed more than just processes that detect signal from a single, individual molecule.

When Dr. Harris was asked additional questions about his own patent that his former company asserted against Illumina, he simply further confirmed that PGI's construction was

erroneous. Step (b) of claim 1 of the '560 patent recites "identifying said single labeled nucleotide." Ex. 17 at claim 1 (JA 695). This language mirrors claim 1 of the '441 patent, which recites "identifying a single biomolecule." Dr. Harris testified that he believes the Illumina system practices step (b), even though the Illumina system detects a signal from multiple nucleotides at the same time:

> Q. Now what about step B, does Illumina do step B?
>
> A. You know, I suppose you could construe that it does because they use multiple color labeling and multiple color detection and so even though they don't do step A, you could argue they do do step B.

Ex. 6 at 105:5-18 (JA 425); *see also id*. at 49:15-50:16 (confirming that in the Illumina platform signal from multiple nucleotides detected) (JA 411-12).

Such testimony confirms that the language "identifying a single biomolecule" is not limited to detecting a signal from a single individual molecule. If such language were so limited, Dr. Harris never would have testified that the parallel language "identifying said single labeled nucleotide" could encompass detecting signal from multiple nucleotides.

3. Plaintiff's Reply Position

(a) PacBio is estopped from collaterally attacking the PTAB's construction of the preamble in this Court.

PacBio argues that collateral estoppel/issue preclusion does not apply because "PGI is now advancing a construction ***different*** from what it presented to the PTAB" and because "PGI is incorrect that a PTAB claim construction . . . that has not been subject to appellate review is sufficient to trigger collateral estoppel." Joint Brief at 29. Neither argument has merit.

(i) PacBio misidentifies the previously-adjudicated issue.

PacBio tries to frame the previously-adjudicated issue as PGI's proposed construction of the preamble, arguing that there is no identity of issues because "PGI advances a construction that

differs from what it previously proposed in the PTAB." Joint Brief at 30. But that conflates the previously adjudicated issue with a party's position on the issue.

As PGI explained in its opening brief, the previously adjudicated issue in this instance was "whether the preamble of claim 1 is limiting and, if so, what it means." Joint Brief at 15. That issue was actually litigated by the parties and there is no dispute that the PTAB decided the issue, finding the preamble limiting and ruling on what it means. Joint Brief at 29-30. Because all of the other requirements for issue preclusion also are met, Joint Brief at 15-19, PacBio is estopped from collaterally attacking the PTAB's ruling, reflected in PGI's proposed construction in this case.

PacBio argues that the "'capability' concept [in the PTAB's ruling] was introduced *sua sponte* by the PTAB in its final written decision" and therefore "PacBio has not had a full and fair opportunity to litigate the issue." Joint Brief at 31. But the "capability concept" is not "the issue" here. The issue here—as it was in front of the PTAB—is how to construe the preamble. To the extent PacBio disagrees with how the PTAB ruled on that issue, it can raise its arguments in the appeal it filed with the Federal Circuit. Issue preclusion, however, prevents PacBio from collaterally attacking the PTAB's ruling in this Court.

PacBio argues that a "difference in terminology between PGI's proposed construction and what appears in the PTAB's decision counsels against applying collateral estoppel," asserting that the PTAB's Final Written Decision "does not recite a 'signal associated with an individual molecule.'" Joint Brief at 31. But the PTAB's Final Written Decision repeatedly discusses detecting signals associated with multiple molecules versus a single molecule. *See, e.g.,* Ex. 1 at 15-16, 18-20, 31, 45-46, 48 (JA at 39-40, 42-44, 55, 69-70, 72). Ultimately, there is no substantive difference between the PTAB's ruling and PGI's proposed construction. If there were such a

difference, the proper course would be to eliminate it, not to permit PacBio's collateral attack on the ruling.[7]

None of the cases cited by PacBio declined to apply issue preclusion on the ground that a party was proposing a different claim construction than it had proposed in an earlier proceeding. In *Jet Inc. v. Sewage Aeration Systems*, the area of law was trademark, not patent, and the court there declined to apply ***claim*** preclusion, not issue preclusion. 223 F.3d 1360, 1361, 1364 (Fed. Cir. 2000). In *UCP International Ltd. v. Balsam Brands Inc.*, the court found it "unnecessary" to decide whether issue preclusion applied to a claim construction order, 787 Fed. App'x. 691, 702 (Fed. Cir. Oct. 7, 2019), and in *In re Koninklijke Philips Patent Litigation*, the court declined to apply collateral estoppel to PTAB claim constructions because the claims were construed under the broadest reasonable construction standard that was applicable in IPRs at the time but is no longer used. No. 18-cv-01885, 2020 WL 2733931 at *1 (N.D. Cal. May 26, 2020).

(ii) Appellate review is not required to trigger issue preclusion based on a PTAB claim construction.

PacBio bizarrely writes: "Federal Circuit law only become 'final' for purposes of preclusion when they are affirmed on appeal." Joint Brief at 33. Although difficult to comprehend, PacBio appears to be arguing that issue preclusion does not apply here because its appeal of the PTAB's construction is still pending. But that is not the law. To the contrary, "[t]he law is well settled that the pendency of an appeal has no effect on the finality or binding effect of a trial court's holding." *Pharmacia*, 170 F.3d at 1381.

None of PacBio's cases articulate any special exception for PTAB decisions or hold that a Final Written Decision from the PTAB can be collaterally attacked in a district court prior to being

[7] PacBio notes that PGI's proposed construction does not refer to "copies" of a biomolecule. That was to avoid confusion. During the IPR proceedings, PacBio suggested that "copies" meant more than just "multiples," "instances," or "units."

affirmed on appeal. Rather, PacBio's cases simply confirm that issue preclusion operates not only at the level of trial courts and tribunals, but also at courts of appeal. Just as a final decision from a trial court or tribunal bars re-litigation of decided issues in trial courts or tribunals, a final decision from a court of appeal prevents parties from re-arguing decided issues in appellate courts.

Accordingly, in *MaxLinear, Inc. v. CF Crespe LLC*, because the Federal Circuit affirmed the unpatentability of claims 1, 17, and 20 in earlier appellate proceedings, issue preclusion collaterally estopped the appellant from continuing to pursue the patentability of the very same claims in yet another Federal Circuit appeal. 880 F.3d 1373, 1376 (Fed. Cir. 2018) ("Both parties agree that those prior decisions, having been affirmed by our court, ***are binding in this proceeding***, as a matter of collateral estoppel, and they could hardly argue otherwise.") (emphasis added).

Likewise, in *XY, LLC v. Trans Ova Genetics*, the Federal Circuit's decision in a separate appeal affirming the invalidity of "the Freezing Patent" claims had "an immediate issue-preclusive effect on any pending or co-pending actions involving the patent" and prevented the appellant from pursuing the patentability of such claims in another appeal before the Federal Circuit. 890 F.3d 1282, 1294 (Fed. Cir. 2018) ("[W]e need not address Trans Ova's invalidity arguments as to the Freezing Patent claims in view of our affirmance today in a separate appeal invalidating these same claims, which collaterally estops XY from asserting the patent in any further proceedings.").

In *Papst Licensing GmbH v. Samsung Electronics America*, the appellant's voluntary dismissal of two appeals involving the same adverse claim construction and factual findings that were being addressed in a third appeal from a Final Written Decision for a related patent resolved those issues against the appellant, prompting the Federal Circuit to summarily affirm the PTAB's decision based on issue preclusion at the appellate level. 924 F.3d 1243, 1250-53 (Fed. Cir. 2019).

In each of these cases, the appellant was of course free to appeal the earlier Federal Circuit's ruling (up to the Supreme Court) but was barred by issue preclusion from re-arguing the issues at the Federal Circuit. Similarly, PacBio is free to appeal the PTAB's Final Written Decision to the Federal Circuit—and is in fact doing so—but is barred by issue preclusion from re-litigating in this Court the issues resolved by the PTAB's decision. None of PacBio's cases hold that issue preclusion does not attach to a PTAB's Final Written Decision until it is affirmed by the Federal Circuit.

PacBio argues that the statutory estoppel provision of 35 U.S.C. § 315(e) "is clear evidence of Congressional intent that PTAB decisions are subject to Federal Circuit oversight[[8]] and should have no preclusive effect unless and until reviewed," Joint Brief at 33, because the statute does not mention collateral estoppel based on claim construction determinations. But PacBio never articulates a reason why any such mention in the statute would be expected. The statute does not purport to catalog all the ways that a petitioner may be estopped or precluded based on a PTAB decision. The statute addresses a narrow, asymmetric estoppel that applies to a petitioner upon issuance of a Final Written Decision regardless of the outcome. Such statutory estoppel adds to—rather than supersedes—the more general doctrine of issue preclusion. Unlike statutory estoppel, issue preclusion is more narrow in that it (1) might not bar petitioners from re-litigating invalidity grounds in a civil action, given the different standard of proof applied by the PTAB, and (2) does not extend to grounds that the petitioner "reasonably could have raised" in the petition but did not raise and therefore were not actually litigated. Accordingly, 35 U.S.C. § 315 expands estoppel and,

[8] PTAB decisions are of course subject to Federal Circuit oversight, as are district court decisions, which do not require appellate review to trigger issue preclusion.

contrary to PacBio's suggestion, actually evidences Congress's intent to prevent re-litigation, not permit re-litigation in the form of collateral attacks on PTAB decisions pending appeal.

PacBio asserts that in *Becton, Dickinson & Company*, Judge Stark "previously rejected the argument that a PTAB claim construction that has not yet been affirmed on appeal has preclusive effect." Joint Brief at 32-33. But Judge Stark simply observed in a footnote that he was "unaware of any binding caselaw holding that a PTAB claim construction ruling has preclusive effect in district court prior to review by the Federal Circuit." *Becton, Dickinson & Co. v. Neumodx Molecular, Inc.*, No. 19-1126, 2021 WL 1854650, at *3 n.2 (D. Del. May 10, 2021). The Court never analyzed the issue based on first principles. *Id.* Moreover, Judge Stark ultimately construed the claim term the same way as the PTAB, though he stated that he was declining to do so "as a matter of collateral estoppel" in part because one of the patents at issue had not been addressed in the PTAB proceedings. *Id.*

PacBio also suggests that *SynQor* supports its position because the case refers to two *inter partes* reexamination decisions that "had not yet become 'final,'" which PacBio characterizes as meaning "reviewed by the Federal Circuit." Joint Brief at 34. But *SynQor* does not address when those decisions became final, and PacBio does not explain how the finality of reexamination decisions is relevant in any event.

(b) If this Court considers the merits, it should reject PacBio's position.

(i) The preambles of the claims are limiting.

Although in the parties' claim construction exchanges PacBio took the position that "[t]he preamble is not limiting," D.I. 56, Ex. A at 3, nowhere in its brief does PacBio argue in favor of, or even mention, that position. Thus, it is undisputed that the preambles of the claims are limiting.

(ii) "An apparatus for identifying a single biomolecule" is capable of detecting a signal associated with an individual biomolecule.

a) The plain language of the preambles supports PGI's proposed construction.

PacBio asserts that PGI "advances no meaningful argument that the claim language supports its construction." Joint Brief at 34. PacBio is incorrect. For example, PGI pointed out that the word "single" in the preamble "is an exclusive word referring to a count of only one, as understood in plain English." Joint Brief at 28. PGI also cited the *On Demand* case, in which the Federal Circuit recognized that the preamble phrase "high speed manufacture of a single copy of a book" limited the claims to exactly that—manufacturing only one copy of a book. *On Demand Machine Corp. v. Ingram Industries, Inc.*, 442 F.3d 1331, 1343 (Fed. Cir. 2006).

PacBio ignores the word "single" in the preamble "[a]n apparatus for identifying a single biomolecule" and focuses on "identifying," asserting that "[t]he term 'identifying' has a plain and ordinary meaning, which is simply to determine what something is." Joint Brief at 35. According to the preamble, however, the "something" that is being identified is a single biomolecule, not multiple biomolecules.

PacBio argues that the preamble "plac[es] no limitation on ***how*** the identification is done" and argues that "one can determine what a molecule is by first copying it and then analyzing a signal from the collection of identical molecules." *Id.* But the preamble expressly states that the object of the "identifying" is a "single biomolecule." "[A]nalyzing a signal from a collection of identical molecules"[9] is not identifying a "single" molecule; it is at most identifying a collection of molecules.

[9] PacBio states that "this is precisely what was described in the prior art Shendure reference and Illumina technology, which was well-known before the '441 patent's 2007 priority date." Joint Brief at 35. PacBio thus acknowledges that it is trying to construe the claims to cover prior art—

PacBio contends that PGI's proposed construction contains a "negative limitation" because it recites an apparatus that "is capable of detecting a signal associated with an individual biomolecule, as opposed to multiple identical biomolecules." Joint Brief at 31. But the "as opposed to" clause simply clarifies that the claimed apparatus must be capable of detecting a signal from "an individual biomolecule," regardless of its other capabilities. In other words, the "as opposed to" clause helps define the required capability of detecting a signal associated with an individual biomolecule but does not exclude other capabilities, such as ***also*** being capable of detecting a signal from multiple identical biomolecules.

PacBio's argument that inclusion of the "as opposed to" clause in PGI's construction somehow "demonstrates that the broad language 'identifying a single biomolecule' otherwise encompasses determining the identity of a single biomolecule from a collection of multiple identical biomolecules" is puzzling. Joint Brief at 36. The "as opposed to" clause is a clarification, not a carve-out. Expressly referring to "an apple, as opposed to an orange," for example, in no way suggests that the term "apple" otherwise encompasses an orange.

b) The dependent claims in no way suggest that the apparatus of claim 1 need not be capable of detecting a signal associated with an individual biomolecule.

PacBio argues that "The Dependent Claims Confirm That Claim 1 Is Intended To Cover Detecting Signal From Multiple Molecules." Joint Brief at 36-41. The argument does not withstand scrutiny, as explained further below. But even if the argument had merit, PacBio fails to explain how claim 1 being broad enough to "Cover Detecting Signal From Multiple Molecules" would be inconsistent with the apparatus of claim 1 also having the required capability of detecting a signal

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something that, to borrow PacBio's turn of phrase—"should raise an immediate red flag." Joint Brief at 3.

associated with an individual biomolecule, as set forth in PGI's proposed construction. Accordingly, PacBio's arguments based on the dependent claims are inapposite.

In any event, neither of the dependent claims on which PacBio relies supports the inferences that PacBio draws from it. Dependent claim 26 recites amplifying a nucleic acid, not detecting a signal from multiple identical nucleic acids. And consistent with at least one embodiment in the specification, dependent claim 30 recites affixing to the linker site "one or more" biomolecules and detecting a signal from one of them, not detecting a signal from multiple identical biomolecules.

i) Dependent claim 26 recites amplifying a nucleic acid, not detecting a signal from multiple identical nucleic acids.

As PacBio acknowledges, Joint Brief at 36, dependent claim 26 depends from claim 16, which recites "[a] method of sequencing a nucleic acid, comprising the steps of: affixing **one nucleic acid** molecule to the linker site of the apparatus of claim 1; and performing nucleic acid sequencing of **the nucleic acid** on the apparatus." The antecedent for "the nucleic acid" is "one nucleic acid." Accordingly, claim 16 expressly recites "performing nucleic acid sequencing of the [one] nucleic acid on the apparatus."

Claim 26 recites "[t]he method of claim 16, wherein the [one] nucleic acid is amplified at the linker site before nucleic acid sequencing"—i.e., before "performing nucleic acid sequencing of the [one] nucleic acid on the apparatus." As the PTAB found, "[t]here is no further indication in the claim language concerning what is done with the amplified nucleic acid molecules." Ex. 1 at 20 (JA at 44).

Nor does the specification of the '441 patent describe the role that amplification can play in connection with the disclosed invention. Indeed, the inventors did not write about amplification

in any of the SUMMARY, the BRIEF DESCRIPTION OF THE DRAWINGS, or the DETAILED DESCRIPTION of the '441 patent.

Although PacBio does not come right out and say so in its opposition brief, PacBio seems to be arguing that it must be inferred from the reference to amplification in claim 26 that the method of claim 16—which expressly recites "performing nucleic acid sequencing of the [one] nucleic acid"—encompasses affixing multiple copies of a nucleic acid to the same linker site and detecting a signal from multiple identical molecules. But the reference to amplification is not inconsistent with PGI's proposed construction. As PacBio acknowledges, Joint Brief at 36-37, PGI's expert Dr. Harris explained that "a person having ordinary skill in the art would have understood that it might be advantageous, for example, to generate multiple copies of a molecule in the vicinity of a linker site en route to attaching one copy of the molecule to each of multiple different apparatuses on the same bioassay substrate, each to be sequenced individually in parallel." Ex. 5 at ¶ 48 (JA 327).

PacBio criticizes Dr. Harris for using the word "speculative" to refer to this potentially advantageous use of amplification, but Dr. Harris explained that he considered it "speculative" because the inventors of the '441 patent "didn't describe how they were going to take advantage of the amplification process," so he could not say "that this is a strategy that was in the mind of the people who wrote the '441 patent." Ex. 6 at 118:16-19, 119:5-9 (JA 429); Joint Brief at 38-39. Thus, ***any*** strategy for taking advantage of the amplification—including the possibility of affixing multiple identical biomolecules to the same linker site and detecting them as an ensemble, as PacBio theorizes—is equally "speculative." Dr. Harris's example simply shows that, contrary to PacBio's assertions, it cannot be inferred from the reference in claim 26 to a nucleic acid being

"amplified at the linker site" that multiple identical nucleic acids are then affixed to the same linker site and detected as an ensemble.

ii) Dependent claim 30 recites affixing to the linker site "one or more" biomolecules, not detecting a signal from multiple identical biomolecules.

Claim 30 recites "[a] method of detecting a biomolecule, comprising the steps of: affixing **one** or more biomolecule to the linker site of the apparatus of claim 1; and detecting **the biomolecule** on the apparatus." Thus, just as claim 16 expressly recites performing nucleic acid sequencing of one nucleic acid, claim 30 expressly recites detecting one biomolecule.

PacBio states that "one or more biomolecule" is the antecedent for "the biomolecule." Joint Brief at 40. Instead of concluding that the singular "the biomolecule" refers to the part of the antecedent reciting "one . . . biomolecule," however, PacBio argues that "the language of claim 30 [] demonstrates that the claims of the '441 patent use the term 'biomolecule' to refer to a ***species*** of molecule." *Id.* But PacBio does not contend that claim 30 uses the term "biomolecule" to refer to a species consistently. Rather, PacBio asserts that the phrase "affixing one or more biomolecule" in claim 30 is not using "biomolecule" to refer to a species, but the phrase "detecting the biomolecule" eleven words later in the same claim is. PacBio fails to justify this inconsistent interpretation. There is a "presumption that the same terms appearing in different portions of the claims should be given the same meaning unless it is clear from the specification and prosecution history that the terms have different meanings at different portions of the claims." *Fin Control Sys. Pty, Ltd. v. Oam, Inc.* 265 F.3d 1311, 1318 (Fed. Cir. 2001).

Claim 30 can readily be understood with reference to the patent specification. The '441 patent describes affixing more than one biomolecule to a linker site and detecting only one of the biomolecules. For example, the patent discloses that a nucleic acid may be affixed to a linker

site indirectly by an intermediate biomolecule—e.g., a polymerase—for identification by sequencing. '441 Patent, 12:1-9, 13:20-52; Ex. 5 at ¶¶ 51-52 (JA 328-29). Nowhere does the '441 patent describe sequencing such a polymerase, or otherwise identifying it.

PacBio does not dispute that a polymerase is a biomolecule according to the plain and ordinary meaning of "biomolecule." Rather, PacBio argues that a biomolecule like polymerase ceases to be a "biomolecule," as that term is used in the claims, when the biomolecule is used to indirectly affix to a linker site another biomolecule (such as a nucleic acid) to be identified. PacBio argues that "[w]hen the claims wish to refer to a molecule that serves this intermediate linking function, it uses a term different from 'biomolecule'"—namely "linking molecule." Joint Brief at 41. But PacBio does not point to any evidence that the patent treats "biomolecule" and "linking molecule" as mutually exclusive. Nor does PacBio point to any special definition of "biomolecule" in the '441 patent or argue any disavowal by the patentee. PacBio never proposed that "biomolecule" should have anything other than its plain and ordinary meaning in these proceedings.

PacBio cites claim 34, which specifies that the detected biomolecule "is affixed to the linker site of the apparatus by a linking molecule." But that does not preclude the "linking molecule" from also being a "biomolecule." Nor does it preclude a "biomolecule" from also being a "linking molecule." And nothing precludes the "linking molecule" in claim 34 from being one of the "one or more biomolecule" referred to in claim 30—e.g., a biomolecule other than the detected biomolecule.

c) The specification supports PGI's construction.

The specification of the '441 patent teaches that identifying a single biomolecule is a fundamental characteristic of the invention. Joint Brief at 22-27. PacBio denies this. Joint Brief at

45. But PacBio does not contest the underlying factual showings that PGI made in support of it. Joint Brief at 24-27.

PacBio nowhere disputes that the "Summary" section of the patent "gives primacy" to detecting single biomolecules, and that by doing so, "strongly indicates" that the invention requires the capability to perform such detection. Joint Brief at 24. PacBio also nowhere disputes that (i) the "Detailed Description" section repeatedly emphasizes the single-molecule nature of the invention, (ii) all of the apparatuses in the figures of the '441 patent are expressly identified as structures for identifying a single biomolecule, (iii) all of the formal "Examples" in the patent describe apparatuses for detecting a single biomolecule and methods for making and using them, including for sequencing a nucleic acid, and (iv) the specification is elsewhere replete with references to the invention identifying a single molecule. Joint Brief at 25-27.

PacBio also does not dispute that the "Background" of the patent emphasizes that devices should be capable of sequencing single molecules to avoid "an 'asynchrony' problem with prior art methods that detected signal from multiple molecules." Joint Brief at 45; *see also* Joint Brief at 24. Rather, PacBio dismisses that disclosure as "at most a potential goal or benefit of the alleged invention," Joint Brief at 45, as if such a goal or benefit could not play a role in revealing a fundamental characteristic of the invention. PacBio also dismisses the disclosure as not rising to the level of a disavowal or disclaimer, though even if true, no disavowal or disclaimer is needed here. *Id.* at 45-46.

Additionally, PacBio does not dispute the "examples where the specification refers to sequencing reactions using 'a single molecule as the template" or the fact "that the '441 patent 'repeatedly emphasizes the single-molecule nature of the invention.'" Joint Brief at 46 (emphasis omitted). Instead, PacBio asserts that "[e]ven to the extent the '441 patent includes embodiments

or examples that involve detecting a signal from an individual biomolecule, and even to the extent those are preferred embodiments, it would be legal error to limit the claims so that they only encompass systems that have that particular feature of the preferred embodiment and exclude from the scope of the claims systems that do not." *Id.* But PGI is not proposing that the Court import into the claims a limitation from a preferred embodiment or exclude systems lacking such a limitation from the scope of otherwise broader claims; rather PGI is proposing that the Court construe the claims according to their own language, which expressly recites "[a]n apparatus for identifying a ***single*** biomolecule." Thus, PacBio's citation to "black letter law that 'claims are not necessarily and not usually limited in scope simply to the preferred embodiment,'" *id.* (quoting *Akamai Techs., Inv. v. Limelight Networks, Inc.,* 805 F.3d 1368, 1375 (Fed. Cir. 2015)), is inapposite. PGI's proposed construction would not be inconsistent with black letter law even if it had the effect of limiting the scope of the claims to a preferred embodiment because "the general rule, of course, is that claims of a patent are not limited to the preferred embodiment, ***unless by their own language***." *Anchor Wall Sys. v. Rockwood Retaining Walls*, 340 F.3d 1298, 1309 (Fed. Cir. 2003) (emphasis added).

PacBio asserts that the patent also discloses embodiments that detect a signal from an ensemble of multiple identical biomolecules. Joint Brief at 42. But PacBio does not establish that the '441 patent actually discloses such embodiments. PacBio asserts that the alleged disclosure is found in the patent's references to use of the invention with a variety of "sequencing modalities" known in the art. Joint Brief at 42. Those modalities describe how a signal can be generated to identify a base of a nucleic acid. The '441 patent discloses three such modalities in a "Sequencing Modalities" section having three subsections entitled "Base Extension Sequencing: Stepwise

Extension," "Sequencing By Synthesis: Multi-step Extension," and "Ligase-Based Sequencing." '441 patent at 12:36-13:51.

Because these modalities were previously used with ensembles of multiple identical molecules, PacBio argues that when the patent refers to the modalities, it is referring to detecting ensembles of molecules. But the modalities simply address the mechanisms of detection, not how many molecules are detected via the same signal. And the '441 patent makes clear that it is disclosing the use of the modalities for single-molecule sequencing. *See, e.g., id.* at 13:32-35 (explaining in the "Base Extension Sequencing" subsection that "the sequence of ***the*** sample nucleic acid is deduced in the 3' to 5' direction, one base at a time"); *id.* at 13: (describing in the "Sequencing By Synthesis" section that "***the*** sample nucleic acid is sequenced essentially continuously by using terminal-phosphate-labeled nucleotides"); *id.* at 14 (stating in the "Ligase-Based Sequencing" section that "[t]he anchor primer and ligated nanomer are then stripped from ***the*** sample nucleic acid, the device is washed, and the process is repeated, querying a different position"); *see also* 12:53-54 ("For all sequencing modalities, the present invention offers the advantage of being able to resequence single molecules.").

Moreover, all of the alleged "embodiments" are found in material that is incorporated by reference in the patent. "[I]ncorporation by reference does not convert the invention of the incorporated patent into the invention of the host patent." *Modine Mfg. Co. v. U.S. Int'l Trade Comm'n*, 75 F.3d 1545, 1553 (Fed. Cir. 1996), *overruled on other grounds by Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 234 F.3d 558 (Fed. Cir. 2000). PacBio identifies no case that even articulates a presumption against, let alone rejects, a claim construction on the ground that it would exclude an alleged "embodiment" not of the inventor's own work, but rather of a third-party publication cited by the inventor in the specification. Such a theory is unmoored

from established principles of claim construction and should be rejected. Even if such an "embodiment" were contemplated by the canons of claim construction, excluding it would not violate those canons because "[i]t is not necessary that each claim read on every embodiment." *Baran v. Med. Dev. Techs., Inc.*, 616 F.3d 1309, 1316 (Fed. Cir. 2010); *Helsmderfer v. Bobrick Washroom Equip., Inc.*, 527 F.3d 1379, 1383 (Fed. Cir. 2008) ("It is often the case that different claims are directed to and cover different disclosed embodiments.").

d) The prosecution history does not support PacBio.

PacBio contends that PGI's construction "is totally undermined by the original application to which the '441 patent claims priority" because "claim 2 of the '652 application recites sequencing 'plural nucleic acids simultaneously' at 'plural separate binding sites,' wherein the 'binding site randomly catches and fixes a nucleic acid to be sequenced on the binding site position.'" Joint Brief at 48. But this sequencing of ***plural*** nucleic acids ***simultaneously*** at ***plural*** binding sites, each fixed with ***a*** nucleic acid does not describe detecting a signal from an ensemble of multiple identical molecules. Rather, it describes the same kind of parallel single-molecule sequencing approach mentioned in the "Summary" section of the patent—"large-scale sequencing reactions, i.e., simultaneously sequencing a large number of different nucleic acid templates," where "[e]ach sequencing reaction uses a single molecule as the template (i.e., single molecule sequencing)." '441 patent at 2:13-18; *see also* Ex. 1 at 18 (JA at 42) (Final Written Decision) ("The Specification of the '441 patent contemplates running myriad optical detection apparatuses in parallel to detect a *single* or individual biomolecule in each such apparatus.").

Moreover, the inclusion in the '652 application of dependent claim 6, which refers to amplification, fails to support PacBio's position for the same reasons that the "amplification" claim

of the '441 patent (claim 26) fails to do so, as discussed above. PacBio's argument that the prosecution history undermines PGI's construction should be rejected.

e) Extrinsic evidence does not support PacBio.

PacBio points out that in IPR2020-01200, "PGI's expert asserted that usage of the term 'single molecule sequencing' in the specification supports its position because 'single molecule sequencing' was a 'term of art' that refers to 'sequencing an individual biomolecule, not multiple copies of a biomolecule together." Joint Brief at 49 (quoting Ex. 5 at ¶ 42 (JA 324)). As PGI previously noted, Dr. Harris's article in SCIENCE from April 2008 supports his assertion because it repeatedly described "single-molecule sequencing" as sequencing an individual molecule. Ex. 19 at 7 (JA 798).

PacBio argues "that 'single molecule sequencing' encompassed more than just processes that detect signal from a single, individual molecule" based on allegations that lawyers for a company named Helicos, where PGI's expert once worked, subsequently alleged in a complaint against Illumina for infringement of an unrelated patent—U.S. Patent No. 7,169,560. Joint Brief at 49. PacBio contends that in the complaint, which was filed after PGI's expert left the company, Helicos lawyers asserted that Illumina's technology was "single molecule DNA sequencing" technology even though "it indisputably is based on detecting signal from multiple copies of a molecule." *Id.* PacBio fails to articulate why these allegations made by lawyers for an unrelated company in a court pleading are supposedly competent evidence of how a POSA would have understood the term "single molecule sequencing."

PacBio tries to piece together a convoluted argument in its favor based on step (b) in claim 1 of the same unrelated patent, arguing that testimony from PGI's expert about that step somehow "confirms that the language 'identifying a single biomolecule' is not limited to detecting a signal from a single individual molecule." Joint Brief at 50. But the testimony that PacBio relies

on is far from clear. *Id.* And in any event, the correct construction of the '441 patent does not depend on whether a claim in an unrelated patent could be construed, in view of its own specification and lexicography, to encompass detecting a signal from multiple molecules. PacBio's argument that extrinsic evidence undermines PGI's construction should be rejected.

4. Defendant's Sur-Reply Position

(a) Collateral Estoppel Does Not Apply

PGI still has fallen far short of meetings its burden of proof on the collateral estoppel issue. As documented below, at least two of the four required elements are not satisfied. Specifically, PGI has not shown that (1) "the issue previously decided is identical with the one presented in the action in question," and (2) "the prior action has been finally adjudicated on the merits." *See RF Delaware*, 326 F.3d at 1261.

(i) The Parties Never Litigated PGI's Newly-Proposed Construction

PGI is incorrect that the issue the PTAB considered is "identical" to the issue before this Court simply because the PTAB construed the preamble, and this Court is now being asked to do the same. The table below shows the constructions the parties proposed in the PTAB alongside the PTAB's final construction and the construction PGI is now proposing:

<table>
<tr><th>PGI's Proposed Construction In The PTAB</th><th>The PTAB's Construction</th><th>PGI's Proposed Construction In This Court</th></tr>
<tr><td>"a structure for identifying an individual biomolecule, as opposed to, for example, multiple copies of a biomolecule in an ensemble"</td><td rowspan="3">"we determine that the preamble of claim 1 is limiting, requires an apparatus capable of identifying a single biomolecule, and provides antecedent basis for 'the biomolecule' as used in the body of the independent claims, which should be read as 'the single biomolecule' introduced in the preamble.</td><td rowspan="3">the apparatus "is capable of detecting a signal associated with an individual biomolecule, as opposed to multiple identical biomolecules"</td></tr>
<tr><th>Pac Bio's Proposed Construction In The PTAB</th></tr>
<tr><td>No construction needed</td></tr>
</table>

As the left-hand column shows, in the IPR, neither party raised the issue of whether claim 1 required the claimed apparatuses to be "capable of" of any particular function. The PTAB, in its final written decision, introduced such a requirement *sua sponte*, a point that PGI does not deny. But, although in this Court PGI picks-up on this "capability" concept, it gives it an entirely new spin: Whereas the PTAB simply required that the claimed apparatus be "capable of" "identifying a single biomolecule," PGI now asks that that the preamble be defined to require that the claimed apparatuses be "capable of" "detecting a signal associated with an individual biomolecule."

Although PGI claims that the "'capability concept' is not 'the issue' here," Joint Brief at 51, this is disingenuous. Whether the claimed apparatus must be "capable" of "detecting a signal associated with an individual biomolecule" is precisely the disputed language in PGI's proposed construction. PGI did not propose this language in the IPR, nor did the PTAB adopt it in its final written decision. As such, the parties in the IPR could not possibly have litigated the claim construction issue currently before the Court. Although PGI tries to frame the "issue" for collateral estoppel purposes as simply whether there was a dispute over the meaning of the preamble, the Court should reject PGI's attempt to impose collateral estoppel by expansively characterizing the

previously disputed issue and otherwise sidestepping the details of what the PTAB actually decided relative to the new language in PGI's construction.

Because PacBio has not had "a full and fair opportunity to litigate the issues" raised by PGI's new claim construction, collateral estoppel does not apply. In similar circumstances, courts have repeatedly held that collateral estoppel does not apply. *See EmeraChem Holdings, LLC v. Volkswagen Group of America, Inc.*, C.A. No. 3:14-cv-132, 2021 WL 5507741, at *10 (E.D. Tenn., Nov. 24, 2021) (declining to apply collateral estoppel to a PTAB construction where the PTAB's construction included a limitation that neither party argued for, explaining that "the construction did not go through the normal adversarial process before becoming part of the Board's final decision."); *UCP*, 787 F. App'x at 706 ("Because the direct connection requirement was added to the construction of 'pivot joint' at summary judgment, collateral estoppel—assuming without deciding that it applies to the Frontgate Order—does not preclude Balsam from challenging that new requirement."); *In re Koninklijke*, 2020 WL 2733931 at *1 ("There is also no evidence that the court addressed constructions for 'identifying,' 'determining,' and 'retrieving.' Accordingly, the claim construction issues were not actually addressed and decided by the Federal Circuit and the Court is not bound by the underlying PTAB interpretations.").

(ii) PGI Has Not Demonstrated That There Was a Final Adjudication On The Merits

PGI has also failed to demonstrate that the PTAB's claim construction ruling represents a final adjudication on the merits sufficient to justify collateral estoppel. Judge Stark previously rejected the ***very same*** argument that PGI now makes for applying collateral estoppel. PGI does not identify any law establishing that Judge Stark's holding in *Becton, Dickinson & Co.* was legal error, or to otherwise support its argument that the PTAB's claim construction ruling in the IPR has preclusive effect on this Court. *See Becton*, 2021 WL 1854650 at *3.

PGI attempts to downplay *Becton*—which is directly on point—by arguing that Judge Stark noted "in a footnote that he was 'unaware of any binding caselaw holding that a PTAB claim construction ruling has preclusive effect in district court prior to review by the Federal Circuit.'" Joint Brief at 54. But PGI's inability to identify any directly applicable case law to support its burden underscores Judge Stark's observation in *Becton*. A PTAB claim construction ruling on appeal to the Federal Circuit is ***not*** a final adjudication on the merits that can collaterally estop a party from challenging the construction in a district court proceeding. *Becton* demonstrates that this Court is not bound by collateral estoppel and may consider the parties' arguments regarding the proper construction of claim 1's preamble. *See Becton*, 2021 WL 1854650 at *3 n.2.

(b) The Preamble Does Not Require That Claimed Apparatuses Be "Capable" Of Detecting Signal From An Individual Biomolecule

While PGI cannot establish that its newly proposed construction—which was neither presented to nor adopted by the PTAB—is warranted by collateral estoppel, its arguments on the merits are equally defective. PGI's proposed construction not only fails to respect the claim language but also ignores embodiments in the specification. As shown below, the claim language and specification mutually reinforce that the patentees wished to ensure that their claims would encompass detection of signal from multiple molecules without imposing any requirement that the claimed apparatuses be "capable" of detecting signal from a single biomolecule.

(i) The Claim Language Confirms That The Claims Encompass Detection Of Signal From Multiple Molecules

PGI contends above it "is proposing that the Court construe the claims according to their own language, which expressly recites '[a]n apparatus, for identifying a ***single*** biomolecule." Joint Brief at 63. Yet, far from construing the claims "according to their own language," PGI drastically rewrites the preamble to include not just new language referring to "signal from an individual

biomolecule" but also a negative limitation reciting "as opposed to multiple identical biomolecules." PGI's need to propose a construction that departs so radically from the original claim language belies any contention that it is respecting the original claim language. Most important, by using its proposed construction to carve out "multiple identical molecules" from the claims, PGI effectively admits that the claim language as drafted is broad enough to encompass detection of signal from multiple molecules.[10]

Nevertheless, after originally saying next to nothing regarding the claim language, PGI now alleges that the word "single" establishes that its construction is correct. *Id.* at 55-56. The preamble, however, states no requirement that the "signal" itself be from a "single" molecule, as recited in PGI's construction. Instead, the preamble merely recites an "apparatus for identifying a single biomolecule," including no limit on ***how*** the single biomolecule is identified. PGI never disputes that to "identify" something is merely to determine what that thing is. The question now is whether the claimed apparatus can "identify a single biomolecule" by, for instance, first making copies of it to amplify the signal. PGI alleges that the claims do not encompass this because "the preamble expressly states that the object of the 'identifying' is a 'single biomolecule.'" *Id.* at 56. But this grammatical structure does not help PGI. The amplification process identifies the "single" original molecule by copying it to aid the detector, just as someone can identify a single sound by replaying it repeatedly, or identify a single bacterium by culturing it. Indeed, the concept of "identifying" a single thing via a process that first amplifies or duplicates the thing to help aid in detection is natural and commonplace.

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[10] PGI attempts to characterize its carve out as a mere "clarification" akin to stating "an apple, as opposed to an orange." Joint Brief at 56. This analogy is inapt. A more appropriate analogy to the instant situation is a patent claim that requires a "fruit" that is supported by a specification which discloses both apples and oranges as embodiments, but then construing the claim term "fruit" to mean "an apple, as opposed to an orange."

The dependent claims reflect this common usage. As PacBio explains above, dependent claim 26 expressly recites that the nucleic acid is first "amplified at the linker site" before sequencing occurs—*i.e.*, that multiple copies of the same identical molecule are created. This confirms that the claimed "identifying" need not take place by detecting a signal from an individual biomolecule and that detecting such a signal is not a fundamental aspect of the invention. If detecting signal from a single individual biomolecule were fundamental, the patentees never would have drafted claims that ***only*** detected signal from multiple molecules.

PGI's response is that, despite its plain language, claim 26 actually only covers detection of signal from a single biomolecule. Joint Brief at 58-60. This dubious argument should be rejected out of hand based simply on the fact that claim 26 recites "amplifying" the biomolecule prior to sequencing. Nevertheless, PGI's logic is that the patent does not "describe the role that amplification can play in connection with the disclosed invention," and the Court should thus look to the "speculative" testimony of its expert to fill the alleged gap in the disclosure to arrive at an understanding of what claim 26 covers. *Id.* PGI is dead wrong on multiple levels.

First, under no circumstances should a court rely upon admitted guesswork by an expert. More importantly, the specification does in fact clearly describes the role of amplification in connection with the disclosed invention. The Shendure article—which is incorporated by reference into the patent specifically for its description of sequencing modalities for use with the alleged invention—describes methods where the "uniting feature" is the use of "isolated (that is, clonal) amplification," after which "each feature to be sequenced contains thousands to millions of copies of an identical DNA molecule[.]" Ex. 7 at 340 (JA 512). As Shendure explains, "the amplification is necessary to achieve sufficient signal for detection." *Id.* PGI's own expert confirmed that in Shendure the identification takes place by detection of signal from multiple

molecules. *See* Ex. 6 at 86:16-21 (JA 421). While PGI asserts that "PacBio never establishes as non-'speculative' the theoretical possibility of affixing to the same linker site all of the biomolecules produced through amplification," Joint Brief at 12, this is what the specification teaches in plain English.

Given this disclosure in the specification, there is no basis whatsoever to credit the "speculative" testimony of PGI's expert that claim 26 refers to some sort of scheme where amplification takes place in "the vicinity" of the linker site "en route" to attaching a single copy of a molecule at each linker site. Joint Brief at 58-59. The patentees included claim 26 not so that they could capture "speculative" processes that PGI's expert would dream up years after filing, but rather to cover the very embodiments that they included in their patent based on pre-existing sequencing technology where signal is detected from multiple molecules.

Claim 30, which refers to affixing "one or more" biomolecule to the "linker site," likewise confirms that the claims encompass detection of signal from multiple molecules. If there is more than one biomolecule at the linker site, there is signal from multiple biomolecules. PGI's theory for this claim is that it actually refers to a using a "biomolecule" as a passive entity that is never detected but merely used to attach another separate "biomolecule." This is without merit. In the claims, the "biomolecule" is the thing that is "identified" or "detected." *See, e.g.*, '441 patent at claim 1 ("An apparatus for identifying a single biomolecule…."); *id.* at claim 9 ("wherein the light detector collects light from the biomolecule"); *id.* at claim 30 ("A method of detecting a biomolecule…."). When the claims wish to refer to a passive connector molecule, they do so using the term "linking molecule." *See id.* at claim 34.

PGI's response to this claim language is that the "patent discloses that a nucleic acid may be affixed to a linker site indirectly by an intermediate biomolecule." Joint Brief at 60-61. This

is incorrect. Not once does the patent refer to an "intermediate" connecting molecule as a "biomolecule." The specification refers to a "biomolecule" 23 times, and in every single instance, the "biomolecule" is the thing that is detected, not the "linking molecule." *See* '441 patent at Title, Abstract, 1:15-23, 2:30-44, 3:11-13, 3:55-57, 4:2-11, 5:49-52, 6:5-6, 7:17-19, 7:53-62, 18:1-11, 18:33-45, 21:1-3, 21:7. Even the Title is clear that the alleged invention is a "Bioassay System Including Optical Detection Apparatuses, and Method for ***Detecting Biomolecules***." The specification of the '441 patent, like the claims, thus distinguishes a "biomolecule" from a "linking molecule" and undermines any contention that a "biomolecule" is a mere passive connector. *See, e.g.*, *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1052 (Fed. Cir. 2010) ("[W]hen a patentee uses a claim term throughout the entire patent specification, in a manner consistent with only a single meaning, he has defined that term 'by implication.'").

(ii) The Specification Establishes That Detection Of Signal From A Single Molecule Is Not "Fundamental"

PGI contends that PacBio fails to dispute that the specification "gives primacy" to detection of signal from single molecules. Joint Brief at 62. Yet, for the specification to limit claims, it must do more than simply "give primacy" to a feature or embodiment. It must disavow or disclaim subject matter or otherwise define the claim terms in a limiting way. That has not happened here. Moreover, PacBio does indeed dispute that the specification "gives primacy" to detection of signal from single molecules. Above, PacBio devotes nearly six pages to detailing the specification's disclosures of several embodiments based on the detection of signal from multiple molecules. Joint Brief at 41-47.

PGI nonetheless asserts that "PacBio does not establish that the '441 patent actually discloses such embodiments." Joint Brief at 63. PGI's assertion that PacBio has failed to substantiate these embodiments is simple willful blindness. The specification expressly describes

"Sequencing Modalities" that can be used either with the claimed "invention" or in "some embodiments," identifying at least three references that set forth such modalities, including the '249 patent, Shendure, and Cheeseman. '441 patent at 12:37-40, 13:2-4. These references—which undisputedly disclose detection of signal from multiple molecules—are incorporated by reference into the '441 patent "for all purposes as well as for the proposition that is recited." *Id.* at 18:51-53. That recited proposition was that the techniques in those references may be used with the alleged invention of the '441 patent. Any suggestion that the patent does not include embodiments based on detection of signal from multiple molecules is without merit.

PGI does not deny that the sequencing references the patent incorporates by reference describe ensemble modalities based on detection of signal from multiple molecules. Instead, PGI asserts that the patent "makes clear" that it actually intends for these modalities to be utilized in a mode where signal is detected from only a single molecule. Joint Brief at 64. Nonsense. In claims 26 and 30, the patent claims that molecules are "amplified" prior to sequencing and that "one or more" biomolecules are placed at the linker site, respectively, such that claimed apparatuses may detect signal from multiple molecules. The only rational conclusion from the specification and claims is not that the patentees intended for the disclosed sequencing modalities based on detection of signal from multiple biomolecules to only be used in a single-molecule mode, but rather that the patentees wished to ensure that their patent covered the ensemble modalities.

PGI cites no evidence in the specification suggesting anything to the contrary. *Id.* PGI cites passages that refer to sequencing "the sample nucleic acid" and then adds its own emphasis to the definite article "the," contending that the definite article somehow shows the patent is describing detection of signal from a single nucleic acid molecule. *Id.* This is misdirection. The term "the sample nucleic acid" is the natural language one would use to describe sequencing

regardless of whether it is based on detecting signal from a single or multiple molecules. The Shendure article also uses the definite article "the" in describing sequencing based on detecting signal from multiple molecules. *See, e.g.*, Ex. 7 at 341 ("Each of the methods discussed so far requires either an in vitro or in situ amplification step, so that ***the*** DNA to be sequenced is present at sufficient copy numbers to achieve the required signal.") (JA 513).

PGI repeats its argument that the claims should be limited to signal from a single molecule because the specification alleges that this overcomes an "asynchrony" problem with the ensemble approach. Joint Brief at 62. But, even if the specification were understood to be disparaging the ensemble approach, this would not justify limiting the claims because, as documented above, the claims and specification are clear that such techniques can be used consistent with the claimed invention. *See, e.g.*, *Epistar Corp. v. Int'l Trade Comm'n*, 566 F.3d 1321, 1335 (Fed. Cir. 2009) ("A patentee's discussion of the shortcomings of certain techniques is not a disavowal of the use of those techniques in a manner consistent with the claimed invention.").

At bottom, PGI's arguments amount to nothing more than an assertion that the claims should be limited because the alleged "nature of the invention" is "single-molecule" and the patent "emphasizes" this as a benefit. *See* Joint Brief at 61-64. Yet, it "is well settled that 'there is no legally recognizable or protected 'essential' element, gist or 'heart' of the invention in a combination patent.'" *Allen Eng'g*, 299 F.3d at 1345. Even if it were the case that detecting signal from an individual biomolecule could somehow be deemed an essential aspect of the alleged invention, this still would not justify limiting the claims because, as proven above, there is no support in the claim language to justify such a requirement. *See, e.g.*, *MBO Labs., Inc. v. Becton, Dickinson & Co.*, 474 F.3d 1323, 1330–31 (Fed. Cir. 2007) ("We sympathize with the district court's choice, since we agree that [the feature] is an essential element of the

invention….However, we cannot endorse a construction analysis that does not identify 'a textual reference in the actual language of the claim with which to associate a proffered claim construction.'").

B. "blocked and labeled nucleotides"

Claim Term	PGI's Position	PacBio's Position
"**blocked and labeled nucleotides"** (claims 21, 22, 24)	No construction necessary.	labeled nucleotides that do not permit further cycles of base extension

1. Plaintiff's Opening Position

The term "blocked and labeled nucleotides" appears in asserted claim 21, which depends from claim 16 and recites:

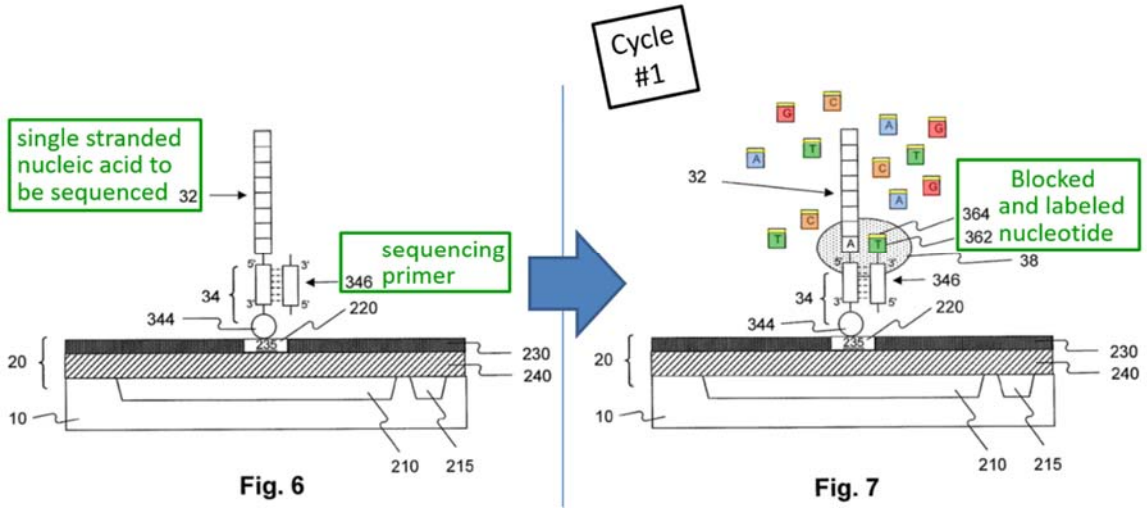
> The method of claim 16, wherein the nucleic acid sequencing is base extension sequencing and includes the step of adding blocked and labeled nucleotides to the apparatus.

Asserted claims 22 and 24 depend from claim 21.

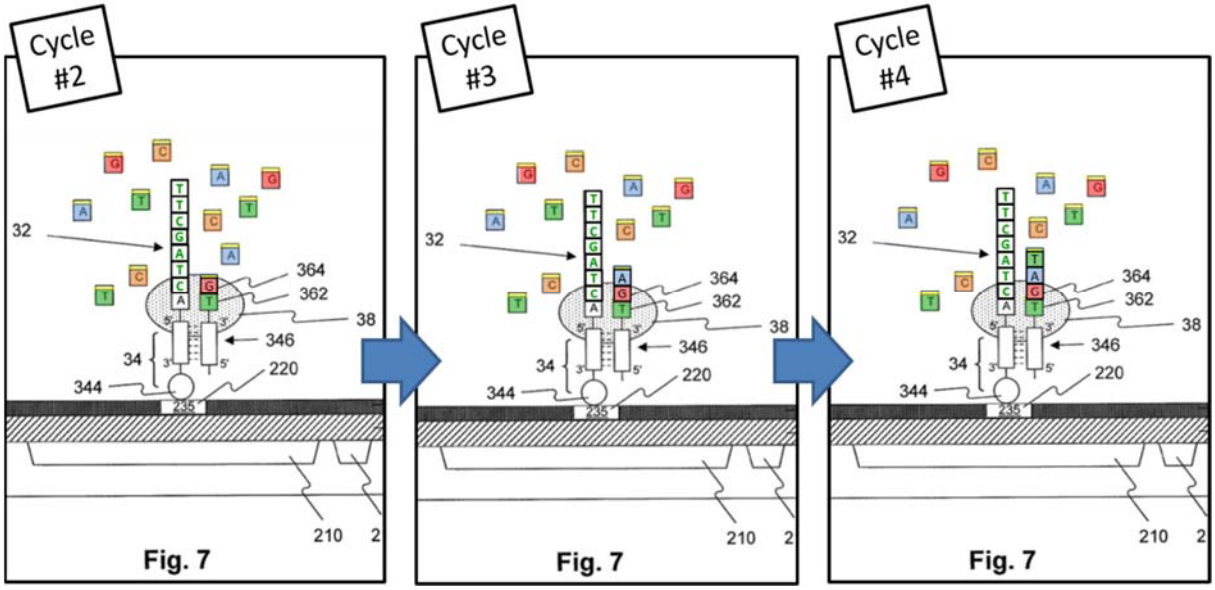
(a) Base Extension Sequencing

The '441 patent refers to "base extension sequencing" as "single base stepwise extensions." '441 patent at 12:43, and dedicates a section to describing the process. *Id*. at 13:1-52. In an example described in the patent, "base extension sequencing begins by attaching . . . a single stranded nucleic acid to be sequenced 32 . . . and a sequencing primer 346 annealed thereto, to a linker site 220, as depicted in FIG. 6." *Id.* at 13:5-10. "[M]odified nucleotides are then applied to the light detection apparatus in a suitable buffer." *Id.* at 13:11-12. "[T]he nucleotides include a covalently linked detectable label, e.g., a fluorescent label, and a blocking group to prevent any secondary extension." *Id.* at 13:15-17. Figure 7 of the patent "illustrates a nucleic acid linked on a linker site of the device after one round of base extension with blocked and labeled nucleotides," *id.* at 3:38-

40, showing "nucleotide 362 with a fluorescent blocking group 364 is added by a DNA polymerase 38 to the 3' end of sequencing primer 346" to complement the A nucleotide on the nucleic acid to be sequenced 32. *Id.* at 13:20-24. Below are FIG. 6. and FIG. 7 of the patent with coloring added.



The complementary T nucleotide "is identified by its label by the corresponding light detector 210." *Id.* at 13:26-28. Because of fluorescent blocking group 364 on the incorporated nucleotide, additional nucleotides cannot be incorporated and "the sequencing pauses." *Id.* at 13:18-19. "The fluorescent label and blocking group are then removed, e.g., by chemical or enzymatic lysis, to permit additional cycles of base extension." *Id.* at 13:28-30.



"By compiling the order of the bases added, the sequence of the sample nucleic acid is deduced in the 3' to 5' direction, one base at a time." *Id*. at 13:32-35.

(b) "blocked and labeled nucleotides" Requires No Construction

The plain and ordinary meaning of "blocked and labeled nucleotides" applies here and no construction is required. PacBio, however, proposes the construction: "labeled nucleotides that do not permit further cycles of base extension."

PacBio's proposed construction should be rejected because it states—without qualification—that blocked and labeled nucleotides "do not permit further cycles of base extension." This contradicts express disclosures of the '441 patent. As described above, for example, the '441 patent expressly teaches that after blocked and labeled nucleotide 362 is incorporated during a cycle of base extension sequencing, "[t]he fluorescent label and blocking group are then removed, e.g., by chemical or enzymatic lysis, to permit additional cycles of base extension." *Id*. at 13:28-30; *see also id.* at 24:63-25:30 (describing adding "four blocked and distinctly labeled DNA nucleotides (A, G, C, T)" to cause "[t]he extension reaction," then "[r]emov[ing] the protection and fluorescent groups" and "[r]epeat[ing] the reaction cycle, to determine the sequence of the nucleic acid"); *id.* at 24:10-62 (Example 5.1) (describing sequential addition of "blocked and labeled adenine," guanine, cytosine, and thymine in a "Base Extension Sequencing Modalit[y]").

A person of ordinary skill in the art would therefore have understood that a "blocked and labeled" nucleotide is capable, as is, of extending a nucleic acid by one base, and is also capable of permitting further cycles of base extension after subsequent modification. Because PacBio's proposed construction suggests the contrary, it should be rejected.

2. Defendant's Answering Position

Claim 21, which depends from claim 16, recites "blocked and labeled nucleotides:"

16. A method of sequencing a nucleic acid, comprising the steps of:
affixing one nucleic acid molecule to the linker site of the apparatus of claim 1; and
performing nucleic acid sequencing of the nucleic acid molecule on the apparatus.

21. The method of claim 16, wherein the nucleic acid sequencing is base extension sequencing and includes the step of adding blocked and labeled nucleotides to the apparatus.

'441 patent at claims 16, 21. The parties' dispute is whether the highly technical term "blocked and labeled nucleotides" should be left undefined so that the jury is left to guess as to its meaning (PGI's proposal) or if it should instead be defined to mean "labeled nucleotides that do not permit further cycles of base extension" (PacBio's proposal). *See* D.I. 56. Because the specification confirms PacBio's construction, it should be adopted. On the other hand, PGI's position that this term should be given no definition whatsoever is contrary to law. *See, e.g.*, *U.S. Surgical Corp. v. Ethicon, Inc*., 103 F.3d 1554, 1568 (Fed. Cir. 1997) (claim construction necessary "when meaning or scope of technical terms and words of art is unclear and in dispute").

Claim 16 recites the use of "base extension sequencing," which the specification describes as "single base stepwise extensions," where the nucleotides include a "blocking group." '441 patent at 12:43; 13:15-19. "Each extension reaction step adds only one type of nucleotide which has a secondary extension protection (blocking) group and a fluorescent label (e.g., Cy5)." *Id*. at 25:45-48. In its brief, PGI includes a description of base extension sequencing, where PGI likewise notes that "[b]ecause of fluorescent blocking group 364 on the incorporated nucleotide, additional nucleotides cannot be incorporated and 'the sequencing pauses.'" Joint Brief at 78.

As the specification's description of "base extension sequencing" makes clear, the purpose of the "blocking group" is to prevent further cycles of base extension sequencing:

> [T]he nucleotides include a covalently linked detectable label, e.g., a fluorescent label, and a blocking group to ***prevent any secondary extension***. Accordingly, ***the sequencing pauses*** after the addition of a single nucleotide…

Id. at 13:15-19 (emphasis added). The specification also describes sequencing "with multiple uninterrupted extensions e.g., ***without the use of blocking groups***," indicating that the "blocking group" is interrupting the base extension. *Id*. at 13:55-57 (emphasis added). As noted, PGI itself acknowledges that the blocking group causes sequencing to pause, stating that "[b]ecause of fluorescent blocking group 364…additional nucleotides cannot be incorporated and 'the sequencing pauses.'" Joint Brief at 78.

Proposing no construction of its own, PGI contends that PacBio's construction "should be rejected because it states—without qualification—that blocked and labeled nucleotides 'do not permit further cycles of base extension'" and that this "contradicts express disclosures of the '441 patent." *Id.* at 19. PGI's position to this effect, however, is based on the logic that a "blocked and labeled" nucleotide is "capable of permitting further cycles of base extension ***after subsequent modification***." *Id.* at 20. Specifically, according to PGI, a "blocked and labeled nucleotide" permits base extension only after the "blocking group" is "removed." *Id.* at 19-20. Once the "blocking group" is removed, however, the nucleotide is not actually a "blocked and labeled nucleotide," but rather just a nucleotide, either labeled or unlabeled. PGI's theory that PacBio's construction is incorrect because it does not encompass the capabilities of chemical compounds that are not actually "blocked and labeled nucleotides" but rather different chemicals that result from the "modification" of "blocked and labeled nucleotides" is without merit.

3. Plaintiff's Reply Position

After dedicating more than 28 pages to arguing in support of its position that "No construction is necessary" for the hotly-disputed preamble of claim 1, PacBio turns around and argues with respect to "blocked and labeled nucleotides" that "PGI's position that this term should be given no definition whatsoever is contrary to law." Joint Brief at 80. PacBio is incorrect.

The parties appear to agree that in the context of "base extension sequencing," as expressly recited in claim 21, "blocked and labeled nucleotides" are designed to be modified so as to permit further cycles of base extension. Joint Brief at 80-82. PGI's concern with PacBio's proposed construction is that it does not capture that versatility. The '441 patent describes "deblocking/delabeling" blocked and labeled nucleotides "to permit additional cycles of base extension." '441 Patent, 13:28-30, 13:35-37. PGI would agree to PacBio's construction with the addition of "absent modification" to the end of it for clarification: "labeled nucleotides that do not permit further cycles of base extension absent modification."

4. Defendant's Sur-Reply Position

Above, PGI asserts that it will now agree to PacBio's construction for "blocked and labeled nucleotides" so long as it is revised to state that such nucleotides may allow further cycles of base extension ***if*** they are modified. Joint Brief at 82. PGI's proposed revision, however, is meaningless and should not be adopted. It goes without saying that if a "blocked and labeled nucleotide" is modified so that it is something else that is no longer "blocked," it may permit further cycles of base extension. While PGI contends that PacBio's construction should be given a slight modification to this effect, it nonetheless agrees that the defining feature of "blocked and labeled nucleotides" is that they do not not permit further cycles of base extension. This is the only construction that is required here.

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August 10, 2022